Respiratory Distress Syndrome: Landmarks in Surfactant Replacement Therapy

- T. Allen Merritt, M.D., MHA
- Emeritus Professor of Pediatrics, LLU Children’s Hospital School of Medicine
  Loma Linda University, Loma Linda, Ca USA

Foundations for Understanding Surfactant Replacement Therapy

In 1929 Kurt von Neergaard, a German physiologist working in Switzerland, evacuated air from an isolated porcine lungs which he then filled with an isotonic gum solution “to eliminate surface tension of the air tissue interfaces” He performed the first pressure-volume during expansion of lungs with both air and liquid.

“Surface tension as a force counteracting the first breath of the newly born should be investigated further.”
RDS & Defective Surfactant

Minimum Surface Tension (dyne/cm²) vs Birth Weight (kg)

Pressure - Volume Curves

Newborn
Stillborn
RDS

Birth Weight (kg)
Volume (ml/kg)
Airway Pressure (cm H₂O)
Incidence of RDS by Gestational Age

Mortality from RDS – US Population Data
Pathophysiology of RDS

- Surfactant deficiency causes:
  - Decreased functional residual capacity
    - Increased chest wall compliance
  - Decreased alveolar surface area
  - Increased airways compliance
  - Gluck et al predicted the probability of RDS based on Lecithin/Sphingomyelin Ratio < 2.0 in Amniotic Fluid
  - Hallman et al reported that predominance of phosphatidylinositol in preterm infants and absence of Phosphatidylglycerol in Amniotic Fluid also predicted RDS with PPV 98% and regardless of maternal illness e.g. especially diabetes, or “stressed fetuses” that was the basis of the “Lung Profile” for antenatal prediction of RDS

Surfactant and the Risk of RDS

- Surfactant very deficient in immature lung (low pool size)
- Towards term, surfactant secreted into amniotic fluid
- Large variation in surfactant pools for a given gestation
- Surfactant components (L/S and PG) predicts the risk of RDS before birth
Human Surfactant Composition

- DPPC – dipalmitoylphosphatidylcholine 50%
- Unsaturated phosphatidylcholine 17%
- Phosphatidyglycerol 17%
- Phosphatidylethanolamine 4%
- Syphingomyelin 2%
- Phosphatidylinositol 2%
- Other phospholipids 3%
- Other lipids 5%
- Serum proteins 8%
- Apoproteins or surfactant specific proteins 2%

PULMONARY SURFACTANT COMPOSITION

- 90 wt% LIPIDS
  - DPPC
  - Unsatuated PC
  - PG
  - Others PL
  - Cholesterol
- 10 wt% PROTEINS
  - 5.0% SP-A
  - 0.7% SP-B
  - 0.8% SP-C
  - 0.5% SP-D
  - 3.0% Plasma Proteins
> **Surfactant Proteins**

<table>
<thead>
<tr>
<th>Present</th>
<th>Characteristics</th>
<th>Main Effects</th>
</tr>
</thead>
</table>
| SP-B & SP-C   | Low molecular weight  
Hydrophobic, SP-B, SP-C  
Essential, SP-B null mice die at birth | Adsorption and spreading of phospholipids,  
Fetal SP-C associated PPROM |

<table>
<thead>
<tr>
<th>Absent</th>
<th>Characteristics</th>
<th>Main Effects</th>
</tr>
</thead>
</table>
| SP-A & SP-D   | High molecular weight  
Hydrophilic, Collectins | Host defense and modulation of inflammatory cytokines in premature labor (from fetal  
Membranes and Placenta |

Van Golde L. Biol Neonate. 1995;67(suppl 1):2-17  
Salminen A. Ph.D. thesis Univ Oulu 2011
Surfactant Protein Function

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SP – A</strong></td>
<td>Tubular myelin, Opsonin, Uptake &amp; secretion of surfactant lipids, Reduces inactivation</td>
</tr>
<tr>
<td><strong>SP – B</strong></td>
<td>Tubular myelin, Lipid adsorption, Minimal surface tension, Reduces inactivation</td>
</tr>
<tr>
<td><strong>SP – C</strong></td>
<td>Affects lipid order, Synergy with SP – B for surface activity, Reduction of inactivation</td>
</tr>
<tr>
<td><strong>SP – D</strong></td>
<td>Opsonin</td>
</tr>
</tbody>
</table>

Surfactant Hydrophobic Proteins—Whitsett and Weaver, NEJM, 2002
Tetsuro Fijiwara from Akito, Japan used a bovine lung homogenate (Surfactant TA) (Lancet 1980) given via endotracheal tube in 10 premature infants with RDS average BW <1250 gm and FiO₂ > .8 (2/10 infants died).

Proof of Principle: Human Surfactant Therapy
Collaboration between Helsinki and San Diego


PROPHYLACTIC TREATMENT OF VERY PREMATURE INFANTS WITH HUMAN SURFACANT


New Engl Journal Medicine, 1986

Era of Surfactant Clinical Trials from 1980-2005 Europe, Canada & USA

Surfactant treatment trials comprised the most studied “drug(s)” used in Neonatal Medicine that has been evaluated by Randomized Controlled Clinical Trials either versus placebo or a comparative surfactants

Surfactant has reduced infant mortality greater than any treatment for infants since the introduction of PEEP.
Landmark studies on surfactant therapy

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Years</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trial with Detergent Alevaire</td>
<td>1948</td>
<td>Gruenwald</td>
</tr>
<tr>
<td>Deficient surface activity in RDS</td>
<td></td>
<td>Avery</td>
</tr>
<tr>
<td>1st RTC with Dipalmitoyl PC</td>
<td>1964</td>
<td>Clements</td>
</tr>
<tr>
<td>L/S ratio, fetal lung maturity</td>
<td></td>
<td>Gluck</td>
</tr>
<tr>
<td>Antenatal glucocorticoid</td>
<td></td>
<td>Liggins</td>
</tr>
<tr>
<td>1st RTC with Dipalmitoyl PC</td>
<td>1970-72</td>
<td></td>
</tr>
<tr>
<td>L/S ratio, fetal lung maturity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal studies on surfactant therapy</td>
<td>1973-83</td>
<td>Robertson, Jobe, Ikegami</td>
</tr>
<tr>
<td>1st trial with DPPC-PG</td>
<td></td>
<td>Fujiwara</td>
</tr>
<tr>
<td>1st RTC with natural surfactant</td>
<td>1980</td>
<td>Morley</td>
</tr>
<tr>
<td>1st RTC with natural surfactant</td>
<td></td>
<td>Hallman, Merritt</td>
</tr>
<tr>
<td>Proph vs Rescue surfactant better</td>
<td></td>
<td>Enhörning</td>
</tr>
<tr>
<td>1st commercial synthetic surfactant</td>
<td>1980</td>
<td></td>
</tr>
<tr>
<td>1st commercial natural surfactant</td>
<td>1990-2</td>
<td></td>
</tr>
<tr>
<td>1st commercial peptide-surfactant</td>
<td>2007</td>
<td></td>
</tr>
</tbody>
</table>

Evolution of Commerically Available Surfactants in USA/Europe

1990
- Exosurf®
- Survanta®
- Infasurf®

1991
- Animal-Derived, Protein-Containing Surfactants

1998
- Curosurf®

1999
- Surfaxin®

2012
- Synthetic, Protein-Containing Surfactant and Aerosurf

4. Data on File, Discovery Laboratories
**Surfactants Used in RCT 1983-2015**

- **Protein-Free**
  - Pumactant (ALEC)
  - Colfosceril palmitate (Exosurf)
  - TurfSurf (Belfast)

- **Peptide Surfactants**
  - Lucinactant (KL4)
  - (Surfaxin)(Aerosurf)
  - rSPC Surf(Venticute)
  - SP C/SP-B analogue CHF5633 (Chiesi)

- **Natural (Amniotic Fluid)**
  - Human AF Surf

- **Lung Lavage Extracts**
  - Calf lung surfactant (BLES), (Infasurf)

- **Minced Lung Extracts**
  - SF-R11 (Alveofact)
  - Beractant (Suvanta)
  - Poractant Alfa (Curosurf)

**Comparative Trials of Animal Derived Surfactants:**

- Speer et al: Curosurf v Survanta
- Halahakoon: Curosurf v Survanta
- Baroutta et al: Curosurf v Survanta v Alveofact
- Ramanathan et al: Curosurf v Survant
- Malloy et al: Curosurf v Survanta
- Bloom et al: Infasurf v Survanta
- Van Overmeire et al: Alveofact v Survanta

Subtle Differences between animal derived surfactants
Curosurf having overall improved survival (but comparisons involved infants of differing GA and Birth Weights)
Multiple vs single dose of natural surfactant in preventing severe RDS and mortality in preterm infants

Pneumothorax

<table>
<thead>
<tr>
<th>Study</th>
<th>Multiple dose</th>
<th>Single dose</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duna 1000</td>
<td>3/12</td>
<td>4/12</td>
<td>1.00</td>
<td>12.0</td>
<td>0.07 (0.07, 2.08)</td>
</tr>
<tr>
<td>Sper 1000</td>
<td>1/10</td>
<td>2/11</td>
<td>0.50</td>
<td>6.0</td>
<td>0.49 (0.21, 1.10)</td>
</tr>
<tr>
<td>Total (5% CI)</td>
<td>10/164</td>
<td>16/241</td>
<td>0.66</td>
<td>101.0</td>
<td>0.51 (0.33, 0.80)</td>
</tr>
</tbody>
</table>

Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Multiple dose</th>
<th>Single dose</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duna 1000</td>
<td>0/37</td>
<td>1/54</td>
<td>0.18</td>
<td>0.0</td>
<td>0.00 (0.00, 0.22)</td>
</tr>
<tr>
<td>Sper 1000</td>
<td>0/39</td>
<td>1/50</td>
<td>0.20</td>
<td>0.0</td>
<td>0.01 (0.00, 0.23)</td>
</tr>
<tr>
<td>Total (5% CI)</td>
<td>0/76</td>
<td>2/104</td>
<td>0.00</td>
<td>100.0</td>
<td>0.83 (0.39, 1.02)</td>
</tr>
</tbody>
</table>

Prophylactic (<1-2 hours) vs selective use of surfactant in preterm infants


1.3 Bronchopulmonary dysplasia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early treatment</th>
<th>Late treatment</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSIBIS 1992</td>
<td>483</td>
<td>1344</td>
<td>1346</td>
<td>90.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1344</td>
<td>1346</td>
<td>90.4%</td>
<td>0.97 [0.88, 1.08]</td>
</tr>
</tbody>
</table>
| Heterogeneity: Not applicable
| Test for overall effect: Z = 0.53 (P = 0.59) |

1.3.2 Animal-derived surfactant

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early treatment</th>
<th>Late treatment</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gortner 1990</td>
<td>36</td>
<td>154</td>
<td>163</td>
</tr>
<tr>
<td>Konishi 1992</td>
<td>6</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Lefort 2003</td>
<td>6</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>205</td>
<td>219</td>
<td>9.9%</td>
</tr>
</tbody>
</table>
| Heterogeneity: Ch^2 = 2.79, df = 2 (P = 0.26); P = 28%
| Test for overall effect: Z = 0.37 (P = 0.71) |
| Total (95% CI)    | 1549            | 1665           | 100.0%                        | 0.97 [0.88, 1.07]             |
| Total events      | 531             | 551            |                               |                               |
| Heterogeneity: Ch^2 = 2.91, df = 3 (P = 0.41); P = 0%
| Test for overall effect: Z = 0.62 (P = 0.53) |

Test for subgroup differences: Ch^2 = 0.04, df = 1 (P = 0.64), P = 0%
### Outcomes associated with surfactant use in clinical practice. Compilation of 5629 VLBW infants from 14 centers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.50 (1.23, 1.86)</td>
</tr>
<tr>
<td>Severe IVH</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>BPD</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>NEC</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>PDA</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Air Leak</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>Apnea</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
</tbody>
</table>

**Adjusted Odds ratios**

Schwartz et al. NEJM 1994

### Comparison of Prophylaxis versus Selective [e.g. Rescue] treatment (Soll, 2006)

<table>
<thead>
<tr>
<th>Event</th>
<th>Prophylaxis</th>
<th>Selective</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.50 (1.23, 1.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe IVH</td>
<td>1.20 (1.04, 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPD</td>
<td>1.20 (1.04, 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC</td>
<td>1.20 (1.04, 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.20 (1.04, 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>1.20 (1.04, 1.38)</td>
<td></td>
<td></td>
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<tr>
<td>Severe ROP</td>
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<tr>
<td>Air Leak</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Apnea</td>
<td>1.20 (1.04, 1.38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analysis 1.1.** Comparison 1: Prophylactic surfactant vs. treatment of established respiratory distress in preterm infants. Outcome 1: Neonatal mortality.
Results of Systematic Reviews from Multiple Surfactants: Natural Protein Containing Surfactants Superior to Non-protein containing surfactants  Meta-Analysis 2014

Multiple trials using both protein-free synthetic surfactant Exosurf, and “natural” minced lung (Beractant, Poractant alfa (Curosurf) or lung wash surfactants (Calfactant, Alveofact, in one or multiple doses. Trials of single versus multiple doses, early surfactant (Prophylaxis) versus later (Rescue surfactant).

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Doses</td>
<td>0.63</td>
<td>0.39-1.02</td>
<td>14 (7-1000)</td>
</tr>
<tr>
<td>Natural Surfactant</td>
<td>0.86</td>
<td>0.76-0.98</td>
<td>50 (20-1000)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>0.61</td>
<td>0.48-0.77</td>
<td>20 (14-50)</td>
</tr>
<tr>
<td>Early INSURE</td>
<td>0.38</td>
<td>0.08-1.81</td>
<td>---</td>
</tr>
</tbody>
</table>

Lessons learned regarding effectiveness and distribution surfactant during administration

- **Property of Surfactant**
  - Surface Activity
  - Volume
  - Rate of admin.
  - Ventilator settings
  - Fluid vol in lung

  **Clinical Effects**
  - Causes rapid adsorption & spreading in airways/lung
  - Higher volumes result in Improved distribution
  - Bolus administration
  - Improves Distribution
  - PIP and PEEP help clear airways of fluid
  - Higher volumes of fetal lung fluid surfactant distribution (e.g. earlier is better)
Effect of Volume on Bolus Surfactant Distribution

Low volume administered: substantial atelectasis persists

Higher volume administered: better distribution, no atelectasis

Pulmonary distribution of surfactant given in bolus doses is better when given in higher volumes


SP-B & SP-C in phospholipids
Structure of KL4 and Phospholipid Membrane Interactions: Mills, F.D. Long, J. et al The Helical Structure of Surfactant Peptide of KL4 When Bound to POPC: POPG Lipid Vesicles, Biochemistry 2008; (47) 8292
KL₄ Functions Like SP-B

Multiple combinations of peptides RL4, KL4, DL4, added to phospholipids DPPC, DOPG, Palmitic Acid, at various concentrations compared to Phospholipids alone, and Phospholipids and SP B or SP C. Phospholipids + KL4 mimicked the biophysical properties of SP B + PL.

Cochrane CG, Revak SD. Science. 1991;254:566-568

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KL₄ Functions Like SPB

Cochrane CG, Revak SD. Science. 1991;254:566-568
**SPB or KL4 Content**

**% of Phospholipid**

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>% of Phospholipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curosurf</td>
<td>0.38%</td>
</tr>
<tr>
<td>Infasurf</td>
<td>0.74%</td>
</tr>
<tr>
<td>Survanta</td>
<td>0.04%</td>
</tr>
<tr>
<td>SURFAXIN</td>
<td>2.67%</td>
</tr>
<tr>
<td>Human Surfactant</td>
<td>2.00%</td>
</tr>
</tbody>
</table>

**Note:** Curosurf mg/kg based on initial dose (2.5ml/kg); SURFAXIN (5.8ml/kg – 175 mg/kg)

**Source:** Curosurf, Infasurf, and SURFAXIN data based on package insert.
Survanta data based on Hottot, et al., 2002, Chemistry & Physics of Lipids 114, 21-34.

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**RCT of Lucinactant (Surfaxis) KL4 Surfactant**

- **SELECT (N=1294)**
- Trial Design-Superiority
- Inclusion Criteria-GA 24-32 wks; BW 600-1250g
- Treatment-Surfaxis 175 mg/kg, Exosurf 62.5 mg/kg, Survanta 100 mg/kg
- Primary Outcomes-Incidence of RDS at 24 hr; RDS related deaths to 14 days

- **STAR (N=252)**
- Trial Design-Non-inferiority
- Inclusion Criteria-GA 24-29 wks; 600-1250 g
- Treatment-Surfaxis vs Curosurf (175 mg/kg), & Beractant (100 mg/kg)
- Primary Outcomes-Incidence of being alive without BPD at 28 days
SELECT TRIAL (Europe, Latin America)

Primary Outcomes

RDS at 24 hours

RDS deaths up to 14 days

P-values adjusted by BW strata and center using logistic regression


Phase III Trials: SELECT Study Primary Efficacy

$\rho = 0.005$

$\rho = 0.001$

$\rho = 0.002$

SURFAXIN

n = 527

Exosurf

n = 509

Survanta

n = 258

RDS at 24 h

RDS-related mortality through day 14
SELECT - BPD at 36 weeks

- **SURFAXIN**
  - n = 527
- **Exosurf**
  - n = 509
- **Survanta**
  - n = 258

Incidence of BPD:
- SURFAXIN: 40.2%
- Exosurf: 45.0%
- Survanta: 42.2%

Survival w/o BPD:
- SURFAXIN: 59.4%
- Exosurf: 53.8%
- Survanta: 56.2%

- \( p = 0.045 \)
- \( p = 0.021 \)


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Sinha, S et al Pediatrics, 2005
Star Trial: Comparison of Lucinactant to Exosurf and Beractant (non inferiority trial)
STAR: Lucinactant vs Beractant

**SURFAXIN vs. Animal-Derived Surfactants**

Short-Term All-Cause Mortality

- **Survanta** (Beractant)
- **Survanta** (Beractant)
- **Survanta** (Beractant)
- **Survanta** (Beractant)

**Day 28**: 21.5% vs. 17.8%
**36 Wk PMA**: 24.1% vs. 20.3%

- *p* < 0.04

PMA = postmenstrual age
PAS 2005: 57: LB16
Survival rate through 1 Year of Life


Analysis 1.1. Comparison 1 Protein containing synthetic surfactant vs animal derived surfactant (all patients), Outcome 1 Mortality at 28 days.

Analysis 1.2. Comparison 1 Protein containing synthetic surfactant vs animal derived surfactant (all patients), Outcome 5 Chronic lung disease or death at 28 days.
Poractant Alfa (Curosurf) Clinical Trials

- **1988 RCT to placebo**: Improved oxygenation, reduced PIE, Pneumothorax, survival
- **1992 RCT Multiple v Single dose**: Improved oxygenation, reduced airleaks, improved survival
- **1993 RCT Early v Late**: Improved survival and reduced severe IVH with early treatment
- **1993 RCT 200 mg v 100 mg**: Improved oxygenation up to 36 hours no other benefits
- **1997,2002 RCT Prophylaxis v Selective**: Infants<31 weeks less severe RDS, less CLD, improved survival with prophylaxis
- **1999 Curosurf & CPAP Combination**: Earlier extubation and may improve survival in infants <30wks
- **1995-2005 Comparative trials**: Curosurf improved survival over ALEC; More Rapid response than Survanta, and may improve survival

Comparative Trials of Animal Surfactants

- Speer et al, 1995       Curosurf v Survanta
- Griese et al, 1995     Alveofact v Survanta
- Halahakoon, 1999       Curosurf v Survanta
- Van Overmeire et al, 1999 Alveofact v Survanta
- Baroutis et al, 2003    Curosurf v Survanta v Alveofact
- Ramanathan et al, 2004  Curosurf v Survanta
- Malloy et al, 2005     Curosurf v Survanta
- Bloom et al, 2005      Infasurf v Survanta

*Major Outcomes differences were that Survival Was Improved with Curosurf (Odds Ratio 1.0 Curosurf vs 1.52 Beractant vs 1.6 InfaSurf)*
Surfactant Treatment of Meconium Aspiration Syndrome: less pneumothorax, fewer needing ECMO El-Shahed, Dargaville, Ohlsson, Soll Cochane Database 2014

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>4</td>
<td>336</td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>0.98 [0.41, 2.39]</td>
</tr>
<tr>
<td>Treatment with ECMO</td>
<td>2</td>
<td>324</td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>0.64 [0.44, 1.01]</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3</td>
<td>236</td>
<td>Risk Difference (N-H, Fixed, 95% CI)</td>
<td>-0.02 [-0.08, 0.05]</td>
</tr>
<tr>
<td>Pulmonary interstitial emphysema</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Air leaks (pneumothorax, pneumomediastinum, interstitial emphysema)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Duration of assisted mechanical ventilation time</td>
<td>3</td>
<td>158</td>
<td>Mean Difference (M, Fixed, 95% CI)</td>
<td>0.62 [-0.41, 1.62]</td>
</tr>
<tr>
<td>Duration of supplemental oxygen (days)</td>
<td>2</td>
<td>97</td>
<td>Mean Difference (M, Fixed, 95% CI)</td>
<td>0.41 [-2.83, 3.64]</td>
</tr>
<tr>
<td>Need for supplemental oxygen at discharge</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Chronic lung disease (age at diagnosis not stated)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Interventricular haemorrhage (any grade)</td>
<td>2</td>
<td>229</td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>0.87 [0.31, 2.49]</td>
</tr>
<tr>
<td>Severe Interventricular haemorrhage</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>1</td>
<td></td>
<td>Mean Difference (M, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

Surfactant Treatment of Meconium Aspiration Syndrome: less pneumothorax, fewer needing ECMO El-Shahed, Dargaville, Ohlsson, Soll Cochane Database 2014

Trials of various Surfactants in Adult Respiratory Distress Syndrome

Failure of large multicenter trial of Venticute (rSPC surfactant) to alter outcomes of ARDS or reduce ventilator days- Spragg et al
**Mean PaO$_2$-FiO$_2$ values**
Control group vs. Venticute (rh SP-C) Surfactant In Adult Patients with ARDS

![Graph showing mean PaO$_2$-FiO$_2$ values for control and surfactant groups.](image)


---

**Number of ventilator free days in the control group and the surfactant group: A Trial Failure!**

![Bar chart showing number of ventilator free days for control and surfactant groups.](image)

Meta-Analysis of ARDS Trials treated with Surfactant (Failure of rhSP-C [Venticute], Exosurf, Beractant)

<table>
<thead>
<tr>
<th>Surfactant Subgroup</th>
<th>Event Rate (Central Events/Total Events)</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.1.1 Exosurf</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venticute</td>
<td>13/34</td>
<td>0.99</td>
<td>8/17</td>
<td>1994</td>
</tr>
<tr>
<td>Exosurf</td>
<td>145/364</td>
<td>0.11</td>
<td>143/281</td>
<td>1996</td>
</tr>
<tr>
<td>Beractant</td>
<td>390/1040</td>
<td>0.00</td>
<td>378/1000</td>
<td></td>
</tr>
<tr>
<td><strong>4.1.2 Natural surfactant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oregon 1997</td>
<td>10/43</td>
<td>0.99</td>
<td>7/15</td>
<td>1997</td>
</tr>
<tr>
<td>Kehl et al. 2000</td>
<td>40/194</td>
<td>0.99</td>
<td>45/102</td>
<td>2000</td>
</tr>
<tr>
<td>Subtotal</td>
<td>56/252</td>
<td>0.99</td>
<td>52/179</td>
<td></td>
</tr>
<tr>
<td><strong>4.1.3 rhSP-C based surfactant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprigge 2003</td>
<td>7/27</td>
<td>0.99</td>
<td>5/13</td>
<td>2003</td>
</tr>
<tr>
<td>Sprigge 2004</td>
<td>34/106</td>
<td>0.99</td>
<td>28/115</td>
<td>2004</td>
</tr>
<tr>
<td>Subtotal</td>
<td>41/133</td>
<td>0.99</td>
<td>33/128</td>
<td></td>
</tr>
</tbody>
</table>

Surfactant Treatment of Meconium Aspiration Syndrome El-Shahed, Dargaville, Ohlsson, Soll Cochrane Database 2014

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mortality</td>
<td>4</td>
<td>324</td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>0.98 [0.94, 1.03]</td>
</tr>
<tr>
<td>2. Treatment with ECMO</td>
<td>2</td>
<td>204</td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>0.94 [0.89, 1.00]</td>
</tr>
<tr>
<td>3. Pneumothorax</td>
<td>3</td>
<td>255</td>
<td>Risk Difference (N-H, Fixed, 5% CI)</td>
<td>-0.02 [-0.06, 0.02]</td>
</tr>
<tr>
<td>4. Pulmonary interstitial emphysema</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5. Air leak pneumothorax, pneumomediastinum, subcutaneous emphysema</td>
<td>4</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6. Duration of assisted mechanical ventilation (days)</td>
<td>3</td>
<td>158</td>
<td>Mean Difference (N, Fixed, 5% CI)</td>
<td>0.80 [-0.81, 0.82]</td>
</tr>
<tr>
<td>7. Duration of supplemental oxygen (days)</td>
<td>2</td>
<td>97</td>
<td>Mean Difference (N, Fixed, 5% CI)</td>
<td>0.40 [-0.63, 1.43]</td>
</tr>
<tr>
<td>8. Need for supplemental oxygen at discharge</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>9. Chronic lung disease (age of diagnosis not stated)</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>10. Interventricular haemorrhage (any grade)</td>
<td>2</td>
<td>229</td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>0.67 [0.31, 1.49]</td>
</tr>
<tr>
<td>11. Severe intraventricular haemorrhage</td>
<td>1</td>
<td></td>
<td>Risk Ratio (N-H, Fixed, 5% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>12. Duration of hospital stay (days)</td>
<td>1</td>
<td></td>
<td>Mean Difference (N, Fixed, 5% CI)</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>
Synthetic surfactant with SP-C and SP-B analogues

CHF5633 (Chiesi Farmaceutici SpA, Parma, Italy) 200mg/kg
- DPPC:POPG 1:1
- Analogue SP-C (1.5%): 33 amino acids
- Analogue SP-B (0.2%): 34 amino acids

• Survanta (Abbott, Columbus, OH) 100 mg/kg
• Fetal lamb model, 124 days, c-section, FiO₂=1.0, Vt=6mL/kg

Sato A et al. PLoSone; 2013, 7(7):39392

Synthetic surfactant with SP-C and SP-B analogues

• New synthetic surfactant was effective on animal model of RDS

Sato A et al. PLoSone; 2013, 7(7):39392
Other Peptide Surfactants in Development or Clinical Trials

- **Chiesi Farmaceutici-SpA**-Peptide Surfactant CHF 5683 containing SP-B (amino and COOH terminus) peptides and SP-C analogues containing KL4-preterm labms studies confirm biologic activity-Seehase, M et al PLOSone 2013
- Walther, FJ et al-lung lavage young rabbits suggest biologic activity-Peer J
- Human Studies are underway (as a liquid)
- **Innovus-So. Africa**-Peptide containing surfactant SP-B/SP-C Animal studies in preterm lambs show similar results to Curosurf Smith 2013, vanZyl et al 2014-adult rabbit lavage-partial restoration of lung function, less lung Inflammation, Human Studies status unknown

**Less Invasive Surfactant Administration (LISA)**

Kribs et al in Germany published encouraging results after using a “feeding tube” inserted through the vocal cords and administering surfactant and AMV (avoidance of mechanical ventilation)
Less Invasive Surfactant Administration (LISA)

- Kribs et al 2010 LISA vs ETT surfactant among infants < 31 weeks: Less MV in first 72 hr 29% vs 53% p < .001, BPD LISA 11% v 18% p < .004
- Göpel et al 2011 LISA vs ET surf/CPAP 26-28 6/7 weeks: Reduced MV on day 2-3 RR .68 (CI 0.42-.0.88) no change in BPD
- Lebermass-Schrefhof et al 2013: LISA vs ET surf/CPAP 23-27 weeks: MV LISA 23% vs ET/CPAP 52% p,.001, no change in BPD
- Kanmaz et al 2013: LISA vs INSURE infants <32 weeks (<72 hr): MV within 72 h: LISA 30% vs INSURE 45% p < .02, BPD LISA 10% INSURE 20% p = .009

LISA in SPONTANEOUSLY BREATHING FETAL LAMBS: LESS surfactant in & POORER distribution, but SIMILAR physiologic effects to intubation and NO Mechanical Ventilation  (Pediatr Res 2014, KRIBS ET AL)
**OptiMIST HOBART METHOD DARGAVILLE ET AL 2013 AND ONGOING INTERNATIONAL TRIAL**

**Aerosolized surfactants – clinical studies**

The only study utilized single naso-pharyngeal (SNP) tube for CPAP and aerosol delivery

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Method</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorch G</td>
<td>Alveofact®</td>
<td>Jet nebulizer 28-35 wks</td>
<td>A-a O₂ gradient, PCO₂ &amp; Silverman score improved SNP tube CPAP</td>
</tr>
<tr>
<td>Arroe M</td>
<td>Exosurf®</td>
<td>Side stream nebulizer prongs CPAP 23-36 wks</td>
<td>No significant benefits</td>
</tr>
<tr>
<td>Berggren E</td>
<td>Curosurf</td>
<td>Jet nebulizer IF CPAP 27-34 wks</td>
<td>No significant benefits</td>
</tr>
<tr>
<td>Finer N</td>
<td>Aerosurf</td>
<td>Aeroneb Pro® prongs CPAP 28-32 wks</td>
<td>Procedure safe</td>
</tr>
</tbody>
</table>

**QUESTION: Was the right patient interface used?**

Mazela et al, Curr Opin Pediatr 2007; 19: 155
Nebulization of Lucinactant: First study using AeroNeb Pro Vibrating Mesh Nebulizer in USA, 17 infants and all showed improvement: Finer, Merritt, Mazela, Henderson, 2010

Aerosurf Aerosolization + CPAP 5 cm at 0.5-hr start and 3-hr Posttreatment in Infant with RDS
Multicenter pilot study of aerosolized lucinactant delivered via nCPAP
(KL4-CPAP-01 Phase 2A)

Clinical Outcomes According to Gestational Age

<table>
<thead>
<tr>
<th></th>
<th>28-29 weeks (n=6)</th>
<th>30-32 weeks (n=11)</th>
<th>All Enrolled (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Survival through day 28</td>
<td>6 (100)</td>
<td>11 (100)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Survival without BPD</td>
<td>5 (83.3)</td>
<td>10 (90.1)</td>
<td>15 (88.2)</td>
</tr>
<tr>
<td>BPD through day 28</td>
<td>1 (16.6)</td>
<td>1 (9.1)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>RDS at 24 hours</td>
<td>3 (50)</td>
<td>1 (9.1)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Intubation/mechanical ventilation through day 28</td>
<td>3 (50)</td>
<td>2 (18.2)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>ET surfactant administration</td>
<td>3 (50)</td>
<td>2 (18.2)</td>
<td>5 (29.4)</td>
</tr>
</tbody>
</table>

QUESTION: What is the best nebulizer to be used?


Aerosolized KL4 surfactant with CAG for RDS

- New aerosol generation and delivery system: CAG and AFFECTAIR™ (AARC, November 2011)
- GA Dated Pregnant Ewe
- Cesarean Delivery
- Preterm Lamb (6 vs. 6)
  - 128-134 d gestation
  - term = 147 +/- 3 d
  - ~28-32 wk human equivalent
  - AEROSURF™ Emitted dose 22.4 mg/min TPL (60% of nominal dose) vs CPAP

Capillary aerosol generator for surfactant aerosolization

- Lucinactant (Surfaxin®, Discovery Laboratories, Inc.)
- Capillary Aerosol Generator (CAG), ventilator connector (Afectair®)
  - MMAD = 1.9 μm ± 0.6 GSD
  - Time = 90 min
  - Emitted dose = 22.4 mg/minTPL
- 128-134 d preterm lambs, tracheo, CPAP

- Better lung aeration
- Lower levels of:
  - MPO,
  - IL-6
  - IL-8

Multicenter Randomized, Open Label, Controlled Trial to Assess the Safety and Toleratibility of Aerosurf® for Inhalation in Preterm Neonates—On going study in US & Europe 29-34 wks
Summary – Surfactant Trials

- Meta-analysis of CPAP vs INSURE show no significant differences in mortality but fewer overall airleaks with INSURE
- LISA and MIST treatment with various surfactants are moving ahead
- RCT trials of Aerosolized Aerosurf® versus CPAP are underway
- RCT trials of other peptide surfactants are underway in Europe and possibly So Africa

Summary – Trials of Aerosol Delivery vs InSure or CPAP

- Neonatologists are ready for true non-invasive surfactant therapy
- There is need to utilized specific aerosol generator and delivery system which can be used for surfactants in combination with positive end-expiratory pressure support
- Surfactants will become the “carrier” of other drugs into the airways and alveoli—to make therapies directed to the lungs more effective
Surfactant Therapy has been a Great Personal Journey permitting me to learn about surfactant, clinical trials, treating babies and making life-long friends in Finland, Poland, United Kingdom, Sweden, and Canada

“I would rather discover a single fact, even a small one, than debate the great issues at length without discovering a thing”—Galileo Galilei

Thank you for your attention.