Clinical Use of Exogenous Surfactant (For Adults Only....)

Is there a future?

Jim Lewis MD, FRCP
Professor of Medicine and Physiology
CRC Calgary, April 26, 2014
Financial Interest Disclosure
(over the past 24 months)
Jim Lewis  MD

• I have no conflict of interest.
Questions/Objectives

1. *What is the problem* with the endogenous surfactant system in adults with ALI/ARDS?
2. Is this enough *rational* for the several large, expensive clinical trials that have been conducted?
3. *Why hasn’t it worked?*
4. *Is there a future* for exogenous surfactant administration in adults?
<table>
<thead>
<tr>
<th>Conducting Zone</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td>Z</td>
<td>1</td>
</tr>
<tr>
<td>BR</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>3</td>
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<tr>
<td>TBL</td>
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<table>
<thead>
<tr>
<th>Transition and Respiratory Zone</th>
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<tr>
<td>RBL</td>
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<td>AD</td>
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<td>AS</td>
<td>19</td>
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<td>22</td>
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<td></td>
<td>23</td>
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</tr>
</tbody>
</table>
Future indication?
Surfactant Composition

- DPPC
- PG
- PI
- S
- PROTEIN
- UNSAT.PC
- CHOL

Categories:
- SP-A
- SP-B
- SP-C
- SP-D
## Exogenous Surfactant Preparations

### Natural Products
- **Survanta**: bovine (tissue)
- **bLES**: bovine (lavage)
- **Infasurf**: bovine (calf lav)
- **Curosurf**: porcine (tissue)
- **Alveofact**: bovine (lavage)
- **HL-10**: porcine (tissue)

### Synthetic Products
- **Surfaxin**: DPPC, KL4
- **Venticute**: DPPC, rSP-C
- **ALEC**: DPPC, PG
- **Exosurf**: DPPC, hexa, tylo
Surfactant Metabolism - Normal Lung

- **Lipids**
  - Phosphatidylcholine (70%)
  - Phosphatidylglycerol (10%)
  - Other lipids (10%)

- **Proteins**
  - SP-A
  - SP-B
  - SP-C
  - SP-D

**TYPE II CELL**

**macrophage**
PULMONARY SURFACTANT

Small Aggregates

Large Aggregates

Surface film

TYPE II CELL
PULMONARY SURFACTANT in ALI

End Result: Impaired function

Small Aggregates Increased
Large Aggregates Decreased
Composition Dysfunctional

Surface film
Surfactant Function/Dysfunction
An optimal surfactant......

• lowers surface tension...
• maintains alveolar stability...
• prevents “leak”......
• maintains lung compliance....
Reduces “surface tension” at air-liquid interface

LaPlace’s Law

\[ \Delta P = \frac{2\gamma}{r} \]

- \( P \) = Pressure
- \( \gamma \) = Surface tension
- \( r \) = Radius
Exogenous Surfactant Administration

...based on biophysical functions
Rational for Exogenous Surfactant in Patients with ARDS

Physiological Rational
1. ↑ lung recruitment – stabilizes alveoli
2. ↓ edema formation ie. $\Delta P = 2\gamma R$

Experimental Rational
1. Surfactant alterations contribute to lung dysfunction
2. Exogenous surfactant improves lung function in animals
3. Exogenous surfactant very effective in preterm humans
Exogenous Surfactant Therapy

For adults......early trials.

1. “Exosurf Trial”
   - multicenter, randomized trial
   - aerosolized Exosurf
   - no difference in mortality (41%)

   Anzueto et al
   NEJM 1996;334:1417-1421

2. “Survanta Trial”
   - multicenter, randomized trial
   - instilled Survanta
   - mortality 17% vs 41%

   Gregory et al
   Am J Respir Crit Care Med 1997;155:1309-1315
Exogenous surfactant therapy for pediatric patients with the acute respiratory distress syndrome

James F Lewis MD FRCPC, Jasvinder S Dhillon MD FRCPC, Ram N Singh MD FRCPC, Craig C Johnson RRT, Timothy C Frewen MD FRCPC
Department of Medicine, St Joseph’s Health Centre, The University of Western Ontario, and Paediatric Critical Care Medicine, Children’s Hospital of Western Ontario, The University of Western Ontario, London, Ontario; and the Paediatric Intensive Care Unit, Children’s Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario

Exogenous Surfactant in Patients with ARDS
Adult Clinical Trials

1. “Exosurf” trial (1996) - 700+ pts, aerosol, ARDS
2. “Survanta” trial (1997) - 60 pts, inst., ARDS
3. “Venticute” trials (2004-08) - 400+ pts, inst., ARDS
4. “HL-10” trial (2009) - 300+ pts, instilled, ARDS

* No significant benefit.....
Exogenous pulmonary surfactant for acute respiratory distress syndrome in adults: A systematic review and meta-analysis

LI-NA ZHANG, JUN-PING SUN, XIN-YING XUE
and JIAN-XIN WANG
# Meta-analysis of Adult Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>surfactant</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Weg 1994</td>
<td>13</td>
<td>34</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Anzueto 1996</td>
<td>145</td>
<td>364</td>
<td>143</td>
<td>361</td>
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<tr>
<td>Gregory 1997</td>
<td>10</td>
<td>43</td>
<td>7</td>
<td>16</td>
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<tr>
<td>Spragg 2003</td>
<td>7</td>
<td>27</td>
<td>5</td>
<td>13</td>
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<tr>
<td>Spragg (Europe SA) 2004</td>
<td>46</td>
<td>118</td>
<td>43</td>
<td>109</td>
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<td>Spragg (NA) 2004</td>
<td>34</td>
<td>106</td>
<td>29</td>
<td>115</td>
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<tr>
<td>Kesecioglu, J 2009</td>
<td>49</td>
<td>164</td>
<td>45</td>
<td>163</td>
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<tr>
<td>Spragg 2011</td>
<td>64</td>
<td>245</td>
<td>69</td>
<td>249</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1101</td>
<td>1043</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>368</td>
<td>349</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 5.23, df = 7 (P = 0.63); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.06 (P = 0.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta-Analysis Zhang et al
Pediatric Calfactant in Acute Respiratory Distress Syndrome trial.

Willson D, and the Pediatric Acute Lung and Sepsis Investigators Network

Pediatr Crit Care Med
2013; 14:657-65

* Only “direct’ lung injuries based on phase II trial…
TABLE 2. Study Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo (n = 53)</th>
<th>Surfactant (n = 56)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>5 (9.4%)</td>
<td>7 (12.2%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Ventilator-free days at 28 d(^a)</td>
<td>17.1 ± 8.6</td>
<td>14.1 ± 9.3</td>
<td>0.08</td>
</tr>
<tr>
<td>PICU-free days at 28 d(^a)</td>
<td>14.8 ± 8.1</td>
<td>10.6 ± 9.2</td>
<td>0.13</td>
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<tr>
<td>Hospital free days at 28 d(^a)</td>
<td>10.4 ± 7.8</td>
<td>6.4 ± 7.8</td>
<td>0.01</td>
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<tr>
<td>Categorical ICU outcomes</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Discharged on no oxygen</td>
<td>28</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Discharged on oxygen only</td>
<td>20</td>
<td>30</td>
<td></td>
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<tr>
<td>Discharged on ventilator</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>3(^b)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Not discharged at 90 d</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>4</td>
<td>3</td>
<td>0.64</td>
</tr>
<tr>
<td>Use of nitric oxide</td>
<td>8</td>
<td>6</td>
<td>0.57</td>
</tr>
<tr>
<td>Median fluid balance/M² day 7</td>
<td>1190</td>
<td>1177</td>
<td>0.21</td>
</tr>
</tbody>
</table>

\(^a\)±sd.  
\(^b\)Two subjects died after discharge but before 90 d.

* Study stopped due to futility
# Exogenous Surfactant Preparations

<table>
<thead>
<tr>
<th>Natural Products</th>
<th>Synthetic Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survanta, bovine (tissue)</td>
<td>Surfaxin, DPPC, KL4</td>
</tr>
<tr>
<td>bLES, bovine (lavage)</td>
<td>Venticute, DPPC, rSP-C</td>
</tr>
<tr>
<td>Infasurf, bovine (calf lav)</td>
<td>ALEC, DPPC, PG</td>
</tr>
<tr>
<td>Curosurf, porcine (tissue)</td>
<td>Exosurf, DPPC, hexa, tylo</td>
</tr>
<tr>
<td>Alveofact, bovine (lavage)</td>
<td></td>
</tr>
<tr>
<td>HL-10, porcine (tissue)</td>
<td></td>
</tr>
<tr>
<td>Study or Subgroup</td>
<td>surfactant</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>Events</td>
</tr>
<tr>
<td>4.1.1 Exosurf</td>
<td></td>
</tr>
<tr>
<td>Weg 1994</td>
<td>13</td>
</tr>
<tr>
<td>Anzueto 1996</td>
<td>145</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>398</td>
</tr>
<tr>
<td>Total events</td>
<td>158</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.37, df = 1</td>
<td></td>
</tr>
<tr>
<td>I² = 0%</td>
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<tr>
<td>4.1.2 natural surfactant</td>
<td></td>
</tr>
<tr>
<td>Gregory 1997</td>
<td>10</td>
</tr>
<tr>
<td>Kesecioglu-J 2009</td>
<td>49</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>207</td>
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<tr>
<td>Total events</td>
<td>59</td>
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<tr>
<td>Heterogeneity: Chi² = 2.71, df = 1</td>
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<tr>
<td>I² = 63%</td>
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<tr>
<td>4.1.3 rSP-C based surfactant</td>
<td></td>
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<tr>
<td>Spragg 2003</td>
<td>7</td>
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<tr>
<td>Spragg (NA) 2004</td>
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<td>Spragg 2011</td>
<td>64</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>496</td>
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<tr>
<td>Total events</td>
<td>151</td>
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<tr>
<td>Heterogeneity: Chi² = 2.11, df = 3</td>
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</tr>
<tr>
<td>I² = 0%</td>
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</tbody>
</table>

Meta-Analysis Zhang et al
Reasons for variable (ie disappointing) results.....

• Different surfactant preparations (ie Exosurf)
• Different delivery techniques (ie aerosol, instillation, positioning, lavage, RM)
• Variable patient population – initial insult and distribution of injury, mortality in control arm
• Severity of illness at time of treatment

• Others?
Timing is everything…..

- Diagnosis of ARDS is not sensitive/specific
- Mechanical ventilation itself impairs surfactant function...very early after the onset
- Very evident in neonatal studies...earlier is better
Surfactant administration at 1 hr vs 4 hrs after whole lung lavage and mechanical ventilation

**Fig. 3.** Oxygenation response of early versus late surfactant treatment in a saline lavage-induced lung injury in adult rabbits. Animals treated at an early stage (1 h post-lavage) of lung injury had significantly higher \( \text{PO}_2 \) values than the later (4 h post-lavage) treatment. \(^a\), \( ^b \) \( p < 0.05 \).
Future Approaches....

• Early/prophylactic treatment - milder injury, uniform distribution, wouldn’t need as much surfactant....aerosol might be best.

• Later/rescue treatment – severe damage, non-uniform distribution, needs LOTS of surfactant....directed instillation/lavage might be best.
BUT........

Will we ever pursue more clinical trials in ALI involving exogenous surfactant for adult patients?
“Other” Functions of Pulmonary Surfactant....

Potential Future Applications
Components of Host Defence

1. Structural & Mechanical

2. Cellular & Humoral
Structural & Mechanical

“Barrier” Functions

- Cough, sneeze, nasopharynx ( > 10 μm)
- Tracheobronchial tree - “filter” ( > 5 μm)
- Mucociliary clearance ( > 2-3μm)
- Particle “entrapment” (< 2-3 μm)
Surfactant affects ciliary function

Surfactant shown to....

1. increase mucociliary transport
2. increase ciliary beat frequency
3. restore damaged ciliary function

Allerga et al Eur J Resp Dis 1985
Kahuta et al Respir Physiol 1991
Top, A: if surfactant phospholipids are not present, or are deficient, the pressure of moisture in the narrow airway section ($R_1 < R_2$) will be less than what it is in the wide section.

- Surfactant maintains the “openess” of a tube.…
- Surfactant alters viscosity of mucous, secretions.…

* Asthma
* Bronchitis
* Cystic Fibrosis
Dr. Sam Schurch
Effects of Surfactant on a Particle

Schurch et al, Pure and Appl Chem 1992
Where...

\[ F_1 = 2\pi R \cdot \gamma_{13} \cdot \sin\phi \cdot \sin(\theta+\phi) \]
\[ F_2 = \frac{4}{3}\pi R^3 \cdot p_2 g \]
\[ F_3 = F_{31} + F_{32} + F_{33} + F_{34} \]

and...

\[ F_{31} = \pi R^2 \cdot (p_3-p_1)g \cdot z_o (\sin\phi)^2 \]
\[ F_{32} = \pi R^3 \cdot (p_3-p_1)g \cdot (\sin\phi)^2 \cos\phi \]
\[ F_{33} = \pi R^3 \cdot (p_3-p_1)g \cdot ((\cos\phi)^3-1) \]
\[ F_{34} = \frac{4}{3} \pi R^3 \cdot p_1 g \]

Schurch et al, Pure and Appl Chem 1992
If particle is not “removed” ..... 

• Surfactant interaction.....direct/indirect
• Activation of cellular/humoral defenses

∴ “Status” of the surfactant system is important
Surfactant as a Carrier

Intratracheal Budesonide Supplementation in Addition to Surfactant Improves Pulmonary Outcome in Surfactant-Depleted Newborn Piglets


Budesonide Added to Modified Porcine Surfactant Curosurf May Additionally Improve Lung Functions in Meconium Aspiration Syndrome

Surfactant as a Carrier

Early Intratracheal Instillation of Budesonide Using Surfactant as a Vehicle to Prevent Chronic Lung Disease in Preterm Infants: A Pilot Study

Yeh et al, Pediatrics 121: e1310-e1318, 2008
Antimicrobial Peptide-Fortified Surfactant for the Treatment of Cystic Fibrosis
Antimicrobial Peptide-Fortified Surfactant Preparation

- Increasing Antibiotic Resistance
- Diminishing Antibiotics Availability
- Drug Delivery
**24h Subculture/ 48h Read**

**Native Bacteria**

- Saline
- CATH-2
- BLES
- CATH-2/ BLES

* p<0.001 vs. Saline

**ATCC Staph Aureus**

- Saline
- CATH-2
- BLES
- CATH-2/ BLES

**ATCC Pseudomonas**

- Saline
- CATH-2
- BLES
- CATH-2/ BLES
Summary

• Surfactant alterations in ALI are complex
• There is GOOD rational for pursuing this Rx
• Surfactant CAN work in ALI....
  ...we just haven’t figured it out!
• Surfactant may be relevant in MANY other diseases
Acknowledgements

- Ruud Veldhuizen
- Lynda McCaig
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