SURFACTANT UPDATE

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Surfactant Update

• Objectives
  – History
  – Meta-analysis of surfactant therapy
  – New synthetic surfactant
  – Genetic disorders of the surfactant proteins
  – Distribution of the surfactant in the lung
  – Clinical trials
History
• In 1929, Kurt Neergaard inflated an excised porcine lung with air and liquid.
  – “Surface tension is responsible for the greater part of total lung recoil compared to tissue elasticity.”
  – “A lower surface tension would be useful for the respiratory mechanism because without it pulmonary retraction might become so great as to interfere with adequate expansion” and
  – “Surface tension as a force counteracting the first breath of newly born should be investigated further.”
Pressure-Volume Relationship in Cat Lungs

Greater transpulmonary pressure is needed when inflated with air.
History

• Pattle in 1958 in England studied the role of antifoam agents in the prevention of pulmonary edema caused by war gases.
  – He suggested that the premature baby has to deal with increased surface forces in the immature lung.
History

• In 1957, in Maryland Clements measured surface tension.

• Avery and Mead published in 1959:
  “Low surface tension in the lining of the lung permits stability of the alveoli at end-expiration. Lacking such a material, the lung is predisposed to atelectasis…”
History

• In 1973 the first surfactant protein was described.

• In 1980, Fujiwara treated premature infants with surfactant.
History

- 1985, small investigator initiated studies found decrease in death and pneumothorax

- Multicenter trials found decreased death and complications
History

- Wide, but still investigational use in 1989
- Synthetic surfactant was approved in US in 1990
- Surfactant from bovine lung was approved in 1991
- Later synthetic surfactants without protein, found to be less effective
- Current research is aiming to develop synthetic surfactants that contain recombinant surfactant proteins
Meta-Analysis of Surfactant Therapy
Main characteristics of surfactants commonly used in studies

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Family</th>
<th>Main phospholipids</th>
<th>Proteins</th>
<th>Phospholipid concentration (mg ml⁻¹)</th>
<th>Suggested dose (ml kg⁻¹)</th>
<th>Phospholipid per dose (mg kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colfoscерil</td>
<td>Synthetic</td>
<td>DPPC</td>
<td>No</td>
<td>13.5</td>
<td>5</td>
<td>67.5</td>
</tr>
<tr>
<td>Pumactant</td>
<td>Synthetic</td>
<td>DPPC, PG</td>
<td>No</td>
<td>40</td>
<td>1.2</td>
<td>100</td>
</tr>
<tr>
<td>Beractant</td>
<td>Animal-derived (bovine)</td>
<td>DPPC, PG</td>
<td>SP-B/SP-C</td>
<td>25</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Calfactant</td>
<td>Animal-derived (bovine)</td>
<td>DPPC, PG</td>
<td>SP-B/SP-C</td>
<td>35</td>
<td>3</td>
<td>105</td>
</tr>
<tr>
<td>Poractant</td>
<td>Animal-derived (porcine)</td>
<td>DPPC, PG</td>
<td>SP-B/SP-C</td>
<td>80</td>
<td>1.25/2.5</td>
<td>100/200</td>
</tr>
<tr>
<td>Lucinactant</td>
<td>Peptide-containing synthetic</td>
<td>DPPC, POPG</td>
<td>KL4 as SP-B</td>
<td>30</td>
<td>5.8</td>
<td>175</td>
</tr>
</tbody>
</table>

Abbreviations: DPPC, dipalmitoylphosphatidylcholine; PG, phosphatidylglycerol; POPG, palmitoyloleylphosphatidylglycerol; SP-B, surfactant protein B; SP-C, surfactant protein C.
## Surfactant Therapy

### Effect on Pneumothorax

<table>
<thead>
<tr>
<th>Types of Studies (#{ of Studies})</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Typical Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic Surfactant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic Surfactant (6)</td>
<td>-0.05 (-0.09, -0.02)</td>
<td></td>
</tr>
<tr>
<td>Natural Surfactant (8)</td>
<td>-0.15 (-0.20, -0.11)</td>
<td></td>
</tr>
<tr>
<td>Surfactant Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic Surfactant (5)</td>
<td>-0.09 (-0.12, -0.06)</td>
<td></td>
</tr>
<tr>
<td>Natural Surfactant (11)</td>
<td>-0.21 (-0.27, -0.16)</td>
<td></td>
</tr>
</tbody>
</table>

Soll, 2000
## Surfactant Therapy

### Effect on Mortality

<table>
<thead>
<tr>
<th>Types of Studies (# of Studies)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Typical Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic Surfactant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic Surfactant (7)</td>
<td>-0.07 (-0.11, -0.03)</td>
<td></td>
</tr>
<tr>
<td>Natural Surfactant (7)</td>
<td>-0.07 (-0.12, -0.03)</td>
<td></td>
</tr>
<tr>
<td>Rescue Surfactant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic Surfactant (6)</td>
<td>-0.05 (-0.07, -0.02)</td>
<td></td>
</tr>
<tr>
<td>Natural Surfactant (11)</td>
<td>-0.10 (-0.14, -0.06)</td>
<td></td>
</tr>
</tbody>
</table>

Soll, 2000
### Surfactant Therapy

#### Effect on BPD or Mortality

<table>
<thead>
<tr>
<th>Types of Studies (№ of Studies)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Typical Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>Prophylactic Surfactant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic Surfactant (4)</td>
<td>-0.04 (-0.10, 0.01)</td>
<td></td>
</tr>
<tr>
<td>Natural Surfactant (7)</td>
<td>-0.10 (-0.16, -0.04)</td>
<td></td>
</tr>
<tr>
<td>Surfactant Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic Surfactant (4)</td>
<td>-0.08 (-0.11, -0.05)</td>
<td></td>
</tr>
<tr>
<td>Natural Surfactant (11)</td>
<td>-0.09 (-0.14, -0.04)</td>
<td></td>
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</tbody>
</table>

**Soll, 2000**
### Prophylaxis of RDS with Natural Surfactant Extracts

<table>
<thead>
<tr>
<th>Outcome (# of Studies)</th>
<th>Typical Risk Difference (95% CI)</th>
<th>Typical Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax (11)</td>
<td>-0.15 (-0.20, -0.11)</td>
<td></td>
</tr>
<tr>
<td>Patent Ductus Arteriosus (12)</td>
<td>0.03 (-0.03, 0.09)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular Hemorrhage (10)</td>
<td>-0.01 (-0.07, 0.05)</td>
<td></td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia (10)</td>
<td>-0.03 (-0.09, 0.03)</td>
<td></td>
</tr>
<tr>
<td>Mortality (11)</td>
<td>-0.07 (-0.12, -0.03)</td>
<td></td>
</tr>
<tr>
<td>BPD or Mortality (11)</td>
<td>-0.10 (-0.16, -0.04)</td>
<td></td>
</tr>
</tbody>
</table>

Soll, 2000
Prophylactic protein free surfactant for preventing morbidity and mortality in preterm infants

• Studies found variable improvement in the respiratory status

• Decrease in the risk of
  – Pneumothorax (typical RR 0.67, 95% CI 0.50, 0.90)
  – PIE (typical RR 0.68, 95% CI 0.50, 0.93)
  – Neonatal mortality (typical RR 0.70, 95% CI 0.58, 0.85)

• No differences in the risk of IVH, NEC, BPD, ROP, CP

• The meta-analysis supports an increase in the risk of PDA (typical RR 1.11, 95% CI 1.00, 1.22)

• Increased risk of pulmonary hemorrhage (typical RR 3.28, 95% CI 1.50, 7.16)

Soll R, Özek E, Cochrane Review 2010
Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome

- Studies found variable improvement in the respiratory status
- Significant reduction in the risk of
  - Pneumothorax (typical RR 0.63, 95% CI 0.53, 0.75)
  - Mortality (typical RR 0.87, 95% CI 0.76, 0.98)
- Natural surfactant is associated with a marginal increase in the risk of IVH (typical RR 1.09, 95% CI 1.00, 1.19) but no increase in grade 3 to 4 IVH
- The meta-analysis supports a marginal decrease in the risk of BPD or mortality (typical RR 0.95, 95% CI 0.90, 1.01)

Soll R, Blanco F, Cochrane Review 2009
Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome

• No significantly different risk of prespecified primary outcomes
  – Mortality at 36 weeks (typical RR 0.81, 95% CI 0.64, 1.03)
  – CLD at 36 weeks (typical RR 0.99, 95% CI 0.84, 1.18)
  – Combined outcome of mortality or CLD at 36 weeks (typical RR 0.96, 95% CI 0.82, 1.12)

• There were also no differences in any of the secondary outcomes regarding complications of prematurity except NEC

• Decrease in the risk of NEC in infants who received protein containing synthetic surfactants (typical RR 0.60, 95% CI 0.42, 0.86)

Pfister RH, Soll R, Wiswell TE, Cochrane Review 2009
New Synthetic Surfactant
New Synthetic Surfactant

• Lucinactant (Surfaxin)
  • 30 mg phospholipids (3/4\textsuperscript{th} DPPC)
  • 4.05 mg palmitic acid
  • KL4 (sinapultide)
    – Synthetic peptide of 21 amino acids
    – Lysine (K), leucine (L)
    – KLLLLKLLLLKLLLLKLLLLK
  – Mimics effect of Sp-B
  – More resistant to inactivation than Sp-B
Summary of the main demographic characteristics of the lucinactant trials

<table>
<thead>
<tr>
<th></th>
<th>SELECT trial</th>
<th></th>
<th>STAR trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lucinactant (n = 527)</td>
<td>Colfosceril (n = 509)</td>
<td>Beractant (n = 258)</td>
<td>Lucinactant (n = 124)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>263 (49.9)</td>
<td>254 (49.9)</td>
<td>129 (50.0)</td>
<td>60 (48.4)</td>
</tr>
<tr>
<td>Birth weight, g, mean (s.d.)</td>
<td>974 (183)</td>
<td>971 (186)</td>
<td>967 (187)</td>
<td>932 (191)</td>
</tr>
<tr>
<td>Gestational age, weeks, mean (s.d.)</td>
<td>28.2 (1.9)</td>
<td>28.2 (2.0)</td>
<td>28.1 (2.1)</td>
<td>26.9 (1.2)</td>
</tr>
<tr>
<td>Apgar score at 5 min*</td>
<td>7 (3–10)</td>
<td>7 (4–10)</td>
<td>7 (4–10)</td>
<td>8 (3–10)</td>
</tr>
<tr>
<td>Prenatal steroid use, n (%)</td>
<td>415 (79.2)</td>
<td>394 (78.5)</td>
<td>191 (74.3)</td>
<td>109 (87.9)</td>
</tr>
</tbody>
</table>

Abbreviations: SELECT, Safety and Effectiveness of Lucinactant versus Exosurf in a Clinical Trial; STAR, Surfaxin in Therapy Against respiratory distress syndrome.

*Median (range).

Moya F., J Perinatol 2009
**Synthetic Surfactant- Lucinactant**

- **SELECT Trial (Safety and Effectiveness of Lucinactant Versus Exosurf in a Clinical Trial)**


  A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants.

  Pediatrics. 2005 Apr;115(4):1018-1029
Synthetic Surfactant- Lucinactant

- Lucinactant reduced significantly the incidence of RDS at 24 hours, compared with colfosceril (39.1% vs. 47.2%; OR: 0.68, 95% CI 0.52, 0.89)
- No significant difference in comparison with beractant (33.3%)
- Lucinactant reduced significantly RDS-related mortality rates by 14 days compared with both colfosceril (OR 0.43, 95% CI 0.25, 0.73) and beractant (OR 0.35 95% CI 0.18, 0.66)
- BPD at 36 weeks postmenstrual age was significantly less common with lucinactant than with colfosceril (40.2% vs. 45.0%; OR: 0.75, 95% CI 0.56, 0.99)
- All-cause mortality rate at 36 weeks postmenstrual age was lower with lucinactant than with beractant (21% vs. 26%; OR: 0.67, 95% CI 0.45, 1.00)
Synthetic Surfactant- Lucinactant

• STAR Trial (Surfaxin Therapy Against Respiratory Distress Syndrome)

Sinha SK, Lacaze-Masmonteil T, Valls i Soler A, et al. for the Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group
A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome.
Pediatrics Vol. 115 No. 4 April 2005, pp. 1030-1038
Synthetic Surfactant- Lucinactant

- At 28 days, survival w/o BPD for lucinactant 37.8%, for poractant alfa 33.1%
- At 36 weeks the rates were 64.7% (lucinactant) and 66.9%
- Mortality rate at 28 days for the lucinactant group was lower than that for the poractant alfa group (11.8% vs 16.1%)
- Mortality rate at 36 weeks 16% (lucinactant) and 18.5%
- No differences in major dosing complications
- No significant differences were observed in the incidences of common complications of prematurity, including IVH, PVL
One-year outcome of the lucinactant trials

• In the SELECT study no difference in survival
• In the STAR trial lucinactant treated patients had significant higher survival (P=0.04)
• In the combined analysis survival was slightly higher in the lucinactant group (P=0.05)
• No significant differences: duration of mechanical ventilation, supplemental oxygen, initial hospitalization
• Post discharge hospitalization incidence did not differ (SELECT)
• No difference in the neurological evaluation at 1-year corrected age (SELECT)

Moya et al., Pediatrics 2007
Genetic disorders of the surfactant proteins
## Comparison of surfactant deficiency syndromes

<table>
<thead>
<tr>
<th></th>
<th>SP-B deficiency</th>
<th>SP-C disease</th>
<th>ABCA3 deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Birth</td>
<td>Birth–adulthood</td>
<td>Birth–childhood</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Recessive</td>
<td>Dominant/sporadic</td>
<td>Recessive</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Loss of function</td>
<td>Gain of function or dominant negative</td>
<td>Loss of function</td>
</tr>
<tr>
<td><strong>Natural history</strong></td>
<td>Lethal</td>
<td>Variable</td>
<td>Often lethal, may be chronic</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochemical</td>
<td>Absence of SP-B and presence of aberrant proSP-C</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>(tracheal aspirate)</td>
<td>Sequence <em>SFTPB</em></td>
<td>Sequence <em>SFTPC</em></td>
<td>Sequence <em>ABCA3</em></td>
</tr>
<tr>
<td>Genetic (DNA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrastructural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(lung biopsy – EM)</td>
<td>Disorganized lamellar bodies</td>
<td>May have cytoplasmic dense aggregates</td>
<td>Small, dense lamellar bodies</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Lung transplantation or compassionate care</td>
<td>Supportive care, lung transplantation if progressing</td>
<td>Consider lung transplantation</td>
</tr>
</tbody>
</table>

Hamvas et al., Neonatology 2007
Surfactant protein B

- Autosomal recessive disorder 1 per million live births
- Over 30 recessive loss-of-function mutations have been identified
- The most common mutation results in 70% of cases and has carrier frequency 1/1000
- To date no spontaneous mutations have been identified
Surfactant protein B

- Absence of SP-B leads to abnormal surfactant composition
  - Decreased phosphatidylglycerol
  - Incompletely processed proSP-C
- In murine models when SP-B expression is about 25% of normal values respiratory failure develops
- In heterozygous siblings or parents of SP-B-deficient infants whose SP-B expression is 50% have normal pulmonary function
Surfactant protein C

- The frequency of this dominant mutation is unknown
- Over 35 dominantly expressed mutations in SFTPC have been identified that cause acute or chronic lung disease
- Age range is from newborn to adult
- 55% of mutations arise spontaneously
- The most common mutation is associated with 25% of the cases of SP-C related disease
Surfactant protein C

• SFTPC mutation results in misfolded proSP-C.
• Surfactant composition and function appears to be mutation dependent
• Clinical presentation and outcomes of lung disease are significantly more variable
ABCA3

- Recessive mutations, the frequency is unknown, but maybe the most common
- ABCA3 is one of a large family of ATP-binding cassette transporters
- Localized to the limiting membrane of lamellar bodies
- Most highly expressed in the lung, but can be found in the heart, brain, pancreas, kidney and platelets
• Over 70 recessive mutations are associated with lethal RDS in newborns and with chronic respiratory insufficiency in children
• BAL of ABCA3-deficient infants had significantly reduced amounts of PC and markedly reduced function
• ABCA3 mediates PC transport into lamellar bodies
• Absence of ABCA3 function may affect SP-B and SP-C trafficking
Distribution of surfactant in the lung
Distribution of surfactant in the lung


Effect of ventilation rate on instilled surfactant distribution in the pulmonary airways of rats

Distribution of surfactant in the lung

- 12 excised rat lungs were suspended vertically
- Single bolus of Survanta mixed with radiopaque tracer was instilled
- Lungs were ventilated with the same tidal volume at rates 20/min or 60/min
- Labeled surfactant was imaged at 30 frames/s with a microfocal X-ray source
Distribution of surfactant in the lung


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Distribution of surfactant in the lung


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Distribution of surfactant in the lung


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Distribution of surfactant in the lung

• At 20 breaths/min the liquid was quickly driven into the gravity-dependent region of the lungs
• At 60 breaths/min the liquid was first deposited on the airway wall and then transported to the gravity-dependent regions over the following breaths
Distribution of surfactant in the lung

- After the 20 breaths the liquid in the 20 breaths/min group was localized in the gravity-dependent region of the lung
- In the 60 breaths/min group the distribution was more uniform throughout the lung
- The cause of the liquid propagation and final liquid distribution results from the interplay of liquid plug dynamics and gravitational effects
Clinical trials

High-versus low-threshold surfactant retreatment for neonatal respiratory distress syndrome


- Relative efficacy of second and third dose of Infasurf was studied
- Patients were randomized to low threshold (FiO$_2$ >30%) and high threshold (FiO$_2$ >40%, MAP >7cmH$_2$O) retreatment groups
- 2484 neonates received first dose; 1267 reached criteria for randomization
- Patients were stratified by whether they received first dose as prophylaxis or rescue and by whether they had complicated lung disease
High-versus low-threshold surfactant retreatment for neonatal respiratory distress syndrome

- Infants allocated in the high threshold group were receiving slightly more oxygen at 72 hours.
- There was no difference in the number receiving mechanical ventilation at 72 hours.
- No difference in requirement for supplemental oxygen or ventilator support at 28 days.
- No difference in O₂ requirement at 36 weeks or in FiO₂ >60% at any time.
- Significantly higher mortality with complicated lung disease in the high-threshold group.
Conclusion

- Equal efficacy can be realized by delaying surfactant retreatment of infants with uncomplicated RDS until they have reached a higher level of respiratory support.
Timing of initial surfactant treatment for infants 23 to 29 weeks' gestation: is routine practice evidence based?

- VON database, 1998-2000, 401-1500 g, gestation 23-29 weeks, 47608 patients in 341 hospitals
- 79% received surfactant
- First dose was administered at a median time 50 min
- Inborn received surfactant earlier, 43 min vs 79 min
- In 2000, 27% of infants received surfactant in the delivery room
Nasal CPAP or intubation at birth for very preterm infants.

- 610 infants, 25-to-28 weeks, randomly assigned to CPAP or intubation and ventilation
- Primary outcome: death or BPD (O₂ need at 36 weeks)
- Secondary outcome: incidence of intubation, reasons for intubation, FiO₂ at 36 weeks, incidence of air leaks, IVH, duration of ventilation and CPAP, length of stay, days to regain birth weight, methylxanthine therapy, postnatal corticosteroid, dose of surfactant
Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators.

Nasal CPAP or intubation at birth for very preterm infants.

- At 36 weeks 33.9% of CPAP had died or BPD, vs 38.9% of the intubation group (odds favoring CPAP, OR 0.80; 95% CI 0.58 to 1.12; P=0.19)
- At 28 days lower risk of death or oxygen need in the CPAP group (OR 0.63; 95% CI 0.46 to 0.88; P=0.006)
- In the CPAP group, 46% were intubated in first 5 days, the use of surfactant was halved
- Incidence of pneumothorax was increased in CPAP group (p<0.001)
- CPAP group fewer days of ventilation
Conclusion

• In infants born at 25-28-weeks’ gestation, early NCPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia
1316 infants

24 0/7 weeks to 27 6/7 weeks

Randomly assigned to intubation and surfactant treatment or CPAP treatment in the delivery room

Primary outcome was death or bronchopulmonary dysplasia
RESULTS:

- No significant difference in primary outcome between CPAP group (47.8%) and surfactant group (51.0%)
- CPAP group patients had
  - Less frequent intubation or postnatal steroid for BPD (P<0.007)
  - Fewer days of mechanical ventilation (P=0.03)
  - Were more likely to be alive and free from the need for mechanical ventilation by day 7 (P=0.01)
- Results support consideration of CPAP as an alternative to intubation and surfactant treatment
Summary

• In recent years there is still intensive research going on to find the optimal respiratory support and treatment for VLBW infants
• New synthetic surfactant products maybe available in the near future
• There is continued research to characterize the optimal delivery mode of exogenous surfactant
• New genetic disorders of surfactant proteins were described and researchers are trying to identify new problems and therapy for these disorders