The Evolution of Surfactant Administration for Respiratory Distress Syndrome of the Premature Newborn

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Disclosure

I have no actual or potential conflicts of interest or financial relationships to disclose in relation to this presentation.

I will be discussing the off-label use of pulmonary surfactant as delivered by unapproved devices. The only FDA-approved device for surfactant administration at present is an endotracheal tube.
Learning objectives

At the conclusion of this program, participants will be able to:

- Describe how administration of exogenous surfactant improves respiratory mechanics and lung function in the premature neonate

- Explain the differences between various exogenous surfactant preparations

- Identify different indications and mechanisms for surfactant administration as well as their advantages and disadvantages
Respiratory Distress Syndrome

First identified as a disease of fetal lungs “not accepting atmospheric air” in 1700s

Hyaline membrane disease – characterized by:
• Hypoinflation
• Homogenous appearance (“ground-glass opacities”) + air bronchograms on film
• Fibrin deposition


Discovery of the pathophysiology of RDS

Avery, 1959: identification of increased lung surface tension – due to decreased protein-laden phospholipid – as causative/associated etiologic agent in RDS

Chemical named pulmonary surfactant

Image: https://collections.countway.harvard.edu/onview/exhibits/show/avery/item/5482
What is a surfactant?

Surfactant = surface-active agent

Chemicals that reduce the surface tension between two adjacent substances
- Wetting agents
- Detergents

Consist of hydrophilic and hydrophobic parts

Image: [https://www.researchgate.net/figure/Water-droplet-without-left-and-with-surfactant-right-Agricultural-surfactants-can_fig3_3419867348.](https://www.researchgate.net/figure/Water-droplet-without-left-and-with-surfactant-right-Agricultural-surfactants-can_fig3_3419867348.)
Pulmonary surfactant

Secreted by type II alveolar cells (pneumocytes)

Consists of two major components:
- Phospholipids (DPPC, others)
  - Reduce surface tension at air-liquid interface
- Proteins (SP-A, SP-B, etc.)
  - Support PL stability
  - Immunological activation
  - Recycling

Lines the interior surface of the alveolar sac

\[
C = \frac{\Delta V}{P_{atv} - P_{pl}}
\]

Functionality of surfactant

- Increases pulmonary compliance
- Decreases alveolar/small airways collapse at the end of expiration (atelectasis)
- Allows for inflation/expansion of collapsed alveoli/segments
- Prevents collapse of smaller alveoli into larger ones

Image: https://www.tumblr.com/mcatmemoranda/179266358111/according-to-the-lw-of-laplace-if-the-surface
**Pathophysiology of RDS**

Immature lung structure and function → decreased endogenous surfactant effect
- Decreased number of type II pneumocytes
- Decreased pool of surfactant (2-10% of term infants)
- Immature surfactant composition

Other factors
- Structural maturity of terminal airways
- Decreased diaphragmatic musculature
- Decreased chest wall rigidity
- Immature respiratory drive

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**Hallmarks of RDS**

- Decreased lung compliance → hypoinflated lungs
- Pulmonary edema ("ground-glass opacities" and "air bronchograms")
- Impaired O$_2$ and CO$_2$ diffusion between pulmonary vasculature and airspaces
- Increased dead space
- Tachypnea, retractions
- Respiratory failure requiring mechanical ventilation

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**Other clinical conditions**

Most common: RDS of the premature infant

Exposure to maternal diabetes: delayed lung maturation

Surfactant inactivation:
- Meconium aspiration syndrome
- Inflammatory lung injury

Genetic mutations associated with surfactant dysfunction
- SP-B
- ABCA3
- SP-C
Treating & preventing RDS

Prevent prematurity

Optimize maternal glucose control in diabetes

Promote surfactant production and maturation
  • Fetal stress *in utero*
  • Maternal antenatal steroids
  • Inflate the lungs (CPAP)
  • Time (4-5 days)

Prevent complications
  • Prevent barotrauma/volutrauma → avoid/minimize MV → permissive hypercapnia, gentle ventilation
  • Support spontaneous breathing → caffeine, avoidance of sedation

Exogenous surfactant therapy

History of surfactant replacement

Various chemical compounds
  • Nebulized tyloxapol detergent mist ("Alevaire")
  • Principal phospholipid in natural surfactant: DPPC

Natural surfactants
  • Preclinical experiments in rabbits and lambs
  • Fujisurf (1980)
    • Saline-extracted minced bovine lung
    • 10 premature infants (GA ~ 28-33 weeks) with HMD
    • Mechanically ventilated on high settings without improvement
    • Instilled via ETT
    • Improved PaO2 and reduced FiO2 in all babies

Effectiveness of surfactant

1980s-90s: trials to prove Fujiwara’s findings

- Fujiwara’s experiment consistently replicated with both natural (animal-derived) and synthetic surfactants
- RCT’s vs. control (no therapy) demonstrated:
  - Improved short-term pulmonary outcomes (oxygenation, incidence of PIE and air leak)
  - Improved survival
  - Modest improvement in rates of BPD and BPD or death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prophylactic Surfactant</th>
<th>Rescue Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Animal Derived</td>
<td>Synthetic</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>8 (0.60 (0.47–0.77))</td>
<td>7 (0.70 (0.58–0.85))</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>9 (0.40 (0.28–0.54))</td>
<td>6 (0.87 (0.50–1.00))</td>
</tr>
<tr>
<td>PIE</td>
<td>6 (0.46 (0.36–0.59))</td>
<td>2 (0.68 (0.50–0.93))</td>
</tr>
<tr>
<td>BPD</td>
<td>8 (0.91 (0.79–1.03))</td>
<td>4 (1.06 (0.85–1.36))</td>
</tr>
<tr>
<td>BPD/Death*</td>
<td>8 (0.80 (0.72–0.88))</td>
<td>4 (0.89 (0.77–1.03))</td>
</tr>
</tbody>
</table>

N, number; PIE, pulmonary interstitial emphysema.
* Defined at 28 d.


Prophylactic vs. selective surfactant

Prophylactic surfactant: all infants born under a certain GA are intubated in the delivery room and given surfactant → prevent RDS from developing

Selective (rescue) surfactant: administered when infant’s respiratory status decompensates to a predetermined level → treatment of established RDS

Both are beneficial! But…

- With the recent (2000 onward) increased use of CPAP in the delivery room, the benefit of prophylactic surfactant in prevention of mortality and BPD disappears;
- In modern trials (i.e. SUPPORT) where antenatal steroid use is high, there is significantly increased BPD in the prophylaxis group

Surfactant preparations

Initial studies performed with “natural surfactant” – animal preparations
• Bulk of RCT’s and subsequent meta-analyses have demonstrated superiority of surfactant generated from minced porcine lung (Curosurf) over other animal-derived surfactants especially at higher dose

First generation synthetic surfactants (colfosceril = Exosurf) were protein-free preparations and had no survival advantage, taken off the market

Second-generation synthetic surfactant (luminactant = Surfaxin) not inferior to natural surfactants but haven’t captured widespread use

<table>
<thead>
<tr>
<th>Ref.</th>
<th>First author</th>
<th>Year</th>
<th>Dose of Curosurf (mg/kg)</th>
<th>Survanta n/N</th>
<th>Surfactant preparations in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Speer</td>
<td>1995</td>
<td>200</td>
<td>1/33</td>
<td>5/40</td>
</tr>
<tr>
<td>45</td>
<td>Halshakoon</td>
<td>1999</td>
<td>100</td>
<td>5/17</td>
<td>3/10</td>
</tr>
<tr>
<td>36</td>
<td>Barouits</td>
<td>2003</td>
<td>100</td>
<td>5/27</td>
<td>6/26</td>
</tr>
<tr>
<td>36</td>
<td>Ramanathan</td>
<td>2004</td>
<td>100</td>
<td>6/96</td>
<td>8/98</td>
</tr>
<tr>
<td>37</td>
<td>Malloy</td>
<td>2005</td>
<td>200</td>
<td>0/29</td>
<td>3/29</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>20/301</td>
<td>33/301</td>
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</tbody>
</table>


Approved surfactant preparations in USA

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Brand Name</th>
<th>Source</th>
<th>Method</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colfosceril palmitate</td>
<td>Exosurf®</td>
<td>Protein-free 100% DPPC</td>
<td>5 mL/kg</td>
<td></td>
</tr>
<tr>
<td>Beractant</td>
<td>Survanta®</td>
<td>Calf lung</td>
<td>Minced</td>
<td>4 mL/kg</td>
</tr>
<tr>
<td>Calfactant</td>
<td>Infasurf®</td>
<td>Calf lung</td>
<td>Lavage</td>
<td>3 mL/kg</td>
</tr>
<tr>
<td>Poractant</td>
<td>Curosurf®</td>
<td>Porcine lung</td>
<td>Minced</td>
<td>2.5 mL/kg</td>
</tr>
<tr>
<td>Lucinactant</td>
<td>Surfaxin®</td>
<td>DPPG + POPC + sinapultide (21-AA peptide mimicking SP-B)</td>
<td>5.8 mL/kg</td>
<td></td>
</tr>
</tbody>
</table>
Indications for surfactant use

At risk preterm infants who:

- Require intubation and mechanical ventilation due to
  - Unstable apnea
  - Respiratory failure necessitating MV for \( O_2 \) delivery or \( CO_2 \) clearance

- Are managed by non-invasive ventilatory support but meet prespecified thresholds for surfactant benefit:
  - \( FiO_2 \) (often 40%)
  - \( PCO_2 \) (often > 65 mmHg following recruitment maneuvers)

- Most effective when administered in the first two hours of life

Avoiding prolonged mechanical ventilation: INSURE

Traditional approach: intubation and mechanical ventilation for infants meeting criteria

INSURE

- Described by Verder et al. in 1992
- Intubate, SURfactant, then Extubate
- Limits exposure to mechanical ventilation
- Limitations
  - Rapidly changing compliance \( \rightarrow \) risk of air leak
  - Poorly characterized \( \rightarrow \) ENSURE
  - Extubation failure (~10%)
  - Concerns about lung injury even with brief exposure to MV


Less invasive methods for surfactant administration

A variety of approaches have been suggested and studied:

- Thin-catheter technique: direct laryngoscopy and surfactant delivery via endotracheal intubation with small-bore tube
- Surfactant delivery via supraglottic/laryngeal airway
- Pharyngeal administration of surfactant
- Nebulized surfactant

Control comparisons either with CPAP alone or INSURE (measuring intubation rates)

Nebulized surfactant

Many putative advantages
- Non-invasive, avoids direct laryngoscopy
- Low equipment costs – everyone has a nebulizer

Few published studies, mostly low-quality

2021 meta-analysis (mostly unreviewed data) suggests that effect is limited to more mature babies and is modest


Pharyngeal instillation of surfactant

Takes advantage of spreading properties of surfactant compounds

Only one RCT (POPART):
- Found no difference compared with CPAP alone


Surfactant via supraglottic airway

SALSA technique: blind insertion of supraglottic airway device (SAD, i.e. laryngeal mask airway) followed by administration via Y-site adapter to spontaneously breathing infant

First described in early 2000s, first RCT in 2013

- Avoids the needs for personnel skilled at laryngoscopy
- Supraglottic airway already a part of NRP training
- Relatively non-invasive
- Maintenance of PEEP

Use cases:
- LMIC → Azerbaijan and Jordan experiences, also Tanzania and Brazil
- HIC: community settings

Use of SALSA

2024 Cochrane systematic review of 510 infants across 8 randomized trials:

- All compared SALSA with endotracheally-administered surfactant
- No head-to-head trials with other less-invasive methods (LISA)
- Results: little to no effect on composite death or BPD outcome, but may reduce need for mechanical ventilation at any time
  - Insufficient data to support or refute SALSA in smallest babies < 1500 grams or 32 weeks GA

Other limitations:

- No availability of supraglottic airways for infants < 1250 grams
- Limited SAD availability at present in LMIC
- Limited surfactant availability especially in LIC
Thin catheter techniques

Most invasive and best studied of the less-invasive approaches

Nomenclature

• LISA: less invasive surfactant administration – Cologne method: flexible catheter (4 Fr feeding tube) inserted below vocal cords using Magill forceps

• Take Care: flexible catheter (shortened 5 Fr feeding tube) inserted below vocal cords without Magill forceps

• MIST: minimally-invasive surfactant therapy – Hobart method: stiff catheter (16 Ga vascular catheter) inserted below vocal cords without Magill forceps

Some evidence that stiff catheter technique is faster and easier

Magill forceps (used for nasal intubation) are not frequently used for neonatal airway instrumentation in USA

Evidence supporting thin catheter techniques

Numerous observational studies as well as RCTs, all in modern era of CPAP-based post-delivery care

2024 umbrella review

Comparator: INSURE

Findings:
• Reduced risk of death or BPD
• Less need for intubation
• Reduced complication rate
• Decreased NEC?

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<tbody>
<tr>
<td>Death or BPD</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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<td>✗</td>
<td>✗</td>
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<tr>
<td>Death</td>
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<tr>
<td>BPD</td>
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<tr>
<td>Intubation (72 hours)</td>
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<td>✗</td>
<td>✗</td>
<td>✗</td>
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<td>✗</td>
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<tr>
<td>IVH (Grade 2 or more)</td>
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<td>✗</td>
<td>✗</td>
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<td>✗</td>
<td>✗</td>
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<tr>
<td>Pneumothorax</td>
<td>✗</td>
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<tr>
<td>NEC</td>
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</tbody>
</table>

Recommendations from consensus bodies

Most recent UK guideline (2019):

<table>
<thead>
<tr>
<th>Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.2</td>
</tr>
<tr>
<td>Give surfactant to preterm babies who need invasive ventilation for stabilisation in the early postnatal period.</td>
</tr>
<tr>
<td>1.2.3</td>
</tr>
<tr>
<td>When giving surfactant to a preterm baby who does not need invasive ventilation, use a minimally invasive administration technique. If this is not possible, for example, in units without the facilities or trained staff to carry out these techniques, use endotracheal intubation to give surfactant, with early extubation afterwards.</td>
</tr>
</tbody>
</table>

European consensus guidelines (2022):

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If a preterm baby &lt;30 weeks of gestation requires intubation for stabilisation, they should be given surfactant (A2).</td>
</tr>
<tr>
<td>2. Babies with RDS needing treatment should be given an animal-derived surfactant preparation (A1).</td>
</tr>
<tr>
<td>3. LISA is the preferred method of surfactant administration for spontaneously breathing babies on CPAP (A1).</td>
</tr>
</tbody>
</table>

Considerations for using thin catheter techniques

When?
- CPAP > 6 cm / FiO₂ > 0.3

Patient selection
- Optimization of non-invasive support
- Avoid using for infants who require mechanical ventilation
  - Rapidly worsening respiratory disease
  - Unstable apnea

Unanswered questions
- Sedation/analgesia
- Co-administration of early caffeine therapy
- Role of video laryngoscopy
- Long term neurodevelopmental outcomes
Our experience

None! Yet…

Preparation stage
- Synthesis of clinical practice guideline
- Availability of equipment
  - Stiff catheter
  - Video laryngoscope
- Training
  - Physician & APP staff
  - RRT
  - RN

Matt’s tips for surfactant success

1. Be prepared for changing lung compliance immediately following surfactant administration. Use a mechanical ventilator (VTV) or T-piece resuscitator to disperse surfactant when delivering via ETT.
2. There is no longer evidence to support position changes while administering divided doses of surfactant.
3. Administer surfactant to intubated preterm babies as early as possible.
4. Premedication strategy should be individualized for each infant’s clinical scenario. One size doesn’t fit all.
5. Eliminate variations in care based on who is the attending physician of the moment. Use prespecified, unit-specific thresholds to determine candidacy for surfactant replacement therapy.
6. Support a culture of team-based care. Flatten existing hierarchies to allow for optimal communication pathways.
Here is the diagram illustrating pulmonary surfactant molecules at the air-water interface in an alveolus. The image shows a cross-sectional view of an alveolus with surfactant molecules, including proteins and phospholipids, arranged at the interface. This diagram is educational and suitable for use in a biology or medical textbook. You can view the image above.