surfactant replacement therapy in neonates

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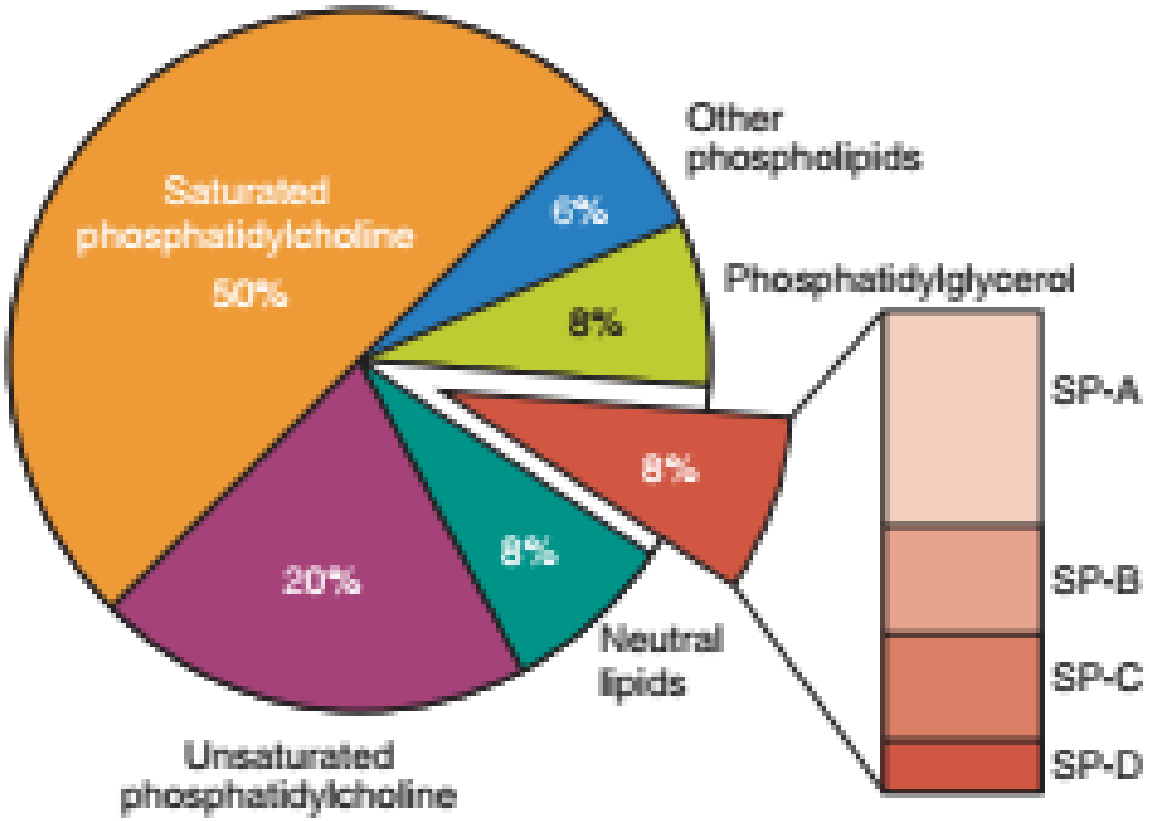
- Pulmonary surfactant discovered in the 1950s
- surfactant has been studied from the 1980s on to treat and prevent respiratory distress syndrome (RDS) in preterm infants
- the first studies of surfactant treatment for neonatal RDS in the 1960s
- surfactant therapy has become the standard therapy of newborn RDS and is deemed one of the most effective and safe medicines in the health system by the WHO.

Components and physiological effects

- Mammalian pulmonary surfactant has similarities in its chemical composition across various species
- With its hydrophobic and hydrophilic properties, it decreases surface tension,

- Surfactant is composed of ~80–85% phospholipids, 5–10% neutral lipids and 8–10% protein, with 5–6% consisting of the four specific surfactant proteins.
- Eighty-five percent of the phospholipid fraction itself consists of phosphatidylcholines, the most important component (40%) with the highest compaction properties being di-palmitoylphosphatidylcholine (DPPC)

- 11% consists of phosphatidylglyerol and phoshatidylinositol, which fluidize the lipid monolayer
- Protein components of surfactant are apolipoproteins and a repertoire of specific proteins, called surfactant protein (SP)-A, -B, -C and -D, which are produced by type II cells and contribute different essential surfactant functions



• **Fig. 62.8** Composition of surfactant. The major component is saturated phosphatidylcholine. The surfactant proteins contribute about 8% to the mass of surfactant.

Surfactant Deficiency

- Surfactant deficiency = decreased compliance
- Decreased compliance = alveolar collapse and loss of FRC
- Loss of FRC = V/Q mismatch
- V/Q mismatch = desaturation, and respiratory distress

Surfactant Therapy for RDS

- Decreases mortality
- Greatest benefit when used with antenatal steroids
- Improvement in compliance, functional residual capacity, and oxygenation
- Reduces incidence of air leaks
- without increasing adverse neurodevelopmental outcomes

Prophylactic versus selective surfactant treatment

- providing exogenous surfactant at birth to infants at risk for RDS
- providing exogenous surfactant to infants with established RDS
- Both strategies have been shown to be effective
- with increasing use of continuous positive airway pressure (CPAP), the benefit of prophylactic surfactant is being questioned
- prophylactic surfactant was associated with a significant increase in BPD, BPD or death at 28 days

Should infants be intubated or not?

- the INSURE (**IN**tubate, **SUR**factant, **E**xtubate) technique
- this strategy is safe and that it may reduce the number of infants intubated and given surfactant
- compared INSURE with CPAP alone
  - appear to trend in favour of INSURE over CPAP alone, particularly in the outcomes of BPD or death, BPD, and air leak
  - Risk factors associated with failure to extubate after INSURE include lower gestational age (GA), lower Apgar score at 5 minutes, and FiO_2 >0.5 before surfactant

Early versus delayed surfactant

- compared early (within the first 2 h of age) to late surfactant administration (delayed until RDS was established, usually 2 h or beyond)
- early surfactant was associated with a significant decrease in mortality, BPD at 36 weeks, BPD or death at 36 weeks, and reduction in the risk of air leak, with no increase in the risk for pulmonary hemorrhage or severe IVH

What type of surfactant is preferable – Natural or synthetic?

- **Synthetic surfactants**
  - First-generation synthetic surfactants are composed of DPPC without surfactant proteins, and they are less effective in reducing ventilation support, pneumothorax, and mortality compared with animal-derived surfactants
    - Exosurf®, approved worldwide and commercially available 1991–2003 contained hexadecanol to promote adsorption and tyloxapol to facilitate dispersion
  - second-generation synthetic surfactant ever tested in infants is lucinactant (Surfaxin), which contains two phospholipids, a fatty acid, and a hydrophobic synthetic peptide to mimic SP-B (KL4 or *sinapultide*) Lucinactant was withdrawn from the market in 2015
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- Lucinactant is currently under development as an aerosolized surfactant (Aerosurf®), having reached preclinical testing
- Lusupultide (Venticute), which contains recombinant SP-C only been tried in adults with acute respiratory distress syndrome
- CHF5633, a third-generation compound combining a 0.2% SP-B analog and a 1.5% SP-C analog in a 1:1 DPPC:palmitoyloleoylphosphatidylglycerol mixture

Animal-derived surfactants

- A wide variety of animal-derived or natural surfactants are available for use
- with significant improvement in oxygenation, ventilation requirements, and reduction of air leak, mortality before hospital discharge
- When comparing different animal-derived surfactants, emerging evidence suggests that porcine minced lung extract, especially in higher dose, may be superior to bovine surfactant for improving acute respiratory status and reducing mortality or BPD in infants with RDS (Level 1a evidence).

- a lower dose of 50 mg/kg, compared to a higher dose of 100 mg/kg.
- Recent guidelines do not recommend repeat doses routinely, but advise that a second (and third) dose should be given to infants with ongoing or progressing respiratory distress

surfactant	source	Phospholipid content mg/ml	Initial (ml/kg)	Dose interval ,hour	Repeat dose
Infasurf (calfactant)	Calf lung	35	3	12	3
Survanta(beractant)	Cow lung	25	4	6	4
Curosurf (poractant alfa)	Pork lung	80	2.5	12	1.25
BLES	Bovin lipid extact	27	5	6	5
Alveofact (bovactant)	Bovin lung	45	1.2	6	1.2
Bracsurf			4	6	4

Dosing and re-dosing surfactant

- re-dosing at low (FiO_2 >0.3 and still requiring intubation) versus high (FiO_2 >0.4 and needing mean airway pressure >7cm H_2O) thresholds, both at least 6 h after the first dose
- delaying re-dosing of surfactant until the infant requires escalated respiratory support is acceptable, except when RDS is complicated by sepsis or perinatal hypoxic-ischemic injury

Newer techniques of surfactant administration

- **Less invasive surfactant administration (LISA)**
  - Compared with mechanical ventilation or CPAP alone, LISA was the non-invasive strategy associated with the lowest likelihood of death or BPD at 36 weeks (Level 2b evidence).
- **Minimally invasive surfactant treatment (MIST)**
  - LISA technique by using a more rigid adult vascular catheter (thus avoiding Magill forceps), known as MIST
  - a high rate of surfactant reflux (66%) was reported
  - loss of surfactant in feeding tubes could be as high as two times that from an ETT

- **Laryngeal mask airway (LMA)**
  - this method is feasible
  - LMA insertion does not require premedication, while INSURE does
- **Pharyngeal surfactant**
  - allows distribution of surfactant to the air–fluid interface during spontaneous breathing

- **Intra-Amniotic Instillation of Surfactant**
  - There is only one feasibility report describing endoscopic delivery of surfactant directly to the fetus during active preterm labor
  - introduced a gas-sterilized intraoperative fiberscope through the cervical canal into the amniotic cavity after spontaneous rupture of membranes during preterm labor
  - it has not been incorporated into clinical practice

- **Nebulization**
  - The only truly non-invasive method of SRT is via nebulization
  - the effect of nebulized surfactant depends on a number of important factors
    - optimal particle size (0.5 to 2.0 μm)
    - stability of the substance after nebulization
    - the loss of particles in relation to an effective dose
  - Earlier clinical studies using jet nebulizers did not show significant clinical benefits
  - A newer device can deliver higher doses of surfactant to the newborn's lungs
  - reduced requirement for intubation in the higher GA subgroup (32^0 to 33^6 weeks) in favour of nebulization (Level 1b evidence)

- Bradycardia
- Hypotension
- Endotracheal tube blockage
- Oxygen desaturation
- Potential for pneumothorax due to sudden changes in pulmonary compliance
- Pulmonary haemorrhage (low incidence, but reported).

- Due to its adsorption and spreading characteristics, surfactant is a potential vehicle for airway-targeted medications
- Addition of budesonide to surfactant does not alter its functional properties and showed beneficial anti-inflammatory effects in animal model

Surfactant for respiratory conditions other than RDS

- Meconium aspiration syndrome (MAS)
- neonatal pneumonia
- Pulmonary hemorrhage

PROCEDURE

- Physician will assess patient eligibility for surfactant administration and write an order for surfactant to be given
- The RRT and registered nurse will perform a baseline patient assessment

- Retrieve surfactant from the freezer and warm to room temperature for no more than 30 min before its use. The vial can be rolled but DO NOT shake it.
- Calculate the amount of surfactant needed.
- Swab the vial rubber cap with an alcohol swab before introducing needle. Fill syringe with surfactant.
- Attached luer lock syringe with medication to luer fitting.
- Attach trach care mac cartridge to Y.
- Before attaching trach care mac to patient, prime the interval volume of the catheter with medication.
- Attach trach care mac adaptor to ventilator circuit and ETT

- pre-oxygenation: the oxygen concentration should be increased to achieve SpO_2 >95% before surfactant delivery.
- Suction ETT and listen to the air entry.
- Lung recruitment manoeuvre: Provide five to 10 inflations with pressures 1 cmH_2O to 2 cmH_2O above previous ventilatory settings to assure some lung recruitment before administration, which would facilitate drug distribution into the pulmonary airways.
- Record all vital signs (heart rate, blood pressure, SpO_2 and $Tc\mathit{P}CO_2$)

When surfactant is instilled into a lung, the distribution results from the following principles:

Property	Effect
Surface activity	Causes rapid adsorption and spreading
Gravity	Surfactant distributed by gravity in large airways
Volume	Higher volumes, cause better distributions
Rate of administration	Rapid administration improves distribution
Ventilator settings	Pressure and PEEP help clear airways of fluid
Fluid volume in the lungs	Higher volumes of fetal lung fluid or edema fluid improves distribution

- Surfactant should be delivered through an in-line catheter with the tip located at the mid trachea level.
- Because the surfactant actually available at the Units is the **bovine lipid extract surfactant** and the dose should be 5 mL/kg (135 mg phospholipids/kg) divided into one or a maximum of two aliquots.
- Mode of delivery: surfactant should be given as bolus infusion (10 s to 20 s).
- Infant should be disconnected from the ventilator and bagged by a physician or another RRT with the flow inflating bag or T-piece device at a rate of 60 inflations/min and pressure necessary to push the surfactant effectively into the pulmonary airways.

- Start the bagging approximately 5 s after initiationof surfactant administration (to give some time for the formation of a fluid plug or column of surfactant into the ETT). The flow rate of the flow inflating bag should be the minimum necessary to provide adequate pressures.
- Infant should be kept in the horizontal position during the entire procedure.
- When using more than one aliquot, a minimum period of 30 s to 60 s between the aliquots should be used if infants remained stable.
- Vital signs and ventilator parameters should be monitored during the delivery process.
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- Details regarding surfactant administration given should be written in the medical records (time, number of aliquots, PIP and PEEP used, vital signs and complications).
- The ETT should not be suctioned for following 2 h unless signs of significant airway obstruction occur.

- **POSTSURFACTANT ADMINISTRATION**
- Registered nurse should record vital signs immediately after administration is completed and every 10 min for the next hour.
- RRT should record ventilator parameters every 15 min for the next hour.

Summary of relevant recommendations

- In neonatal care settings where continuous positive airway pressure (CPAP) is routinely used to stabilize preterm infants and when the rate of antenatal corticosteroid administration has been high (> 50%), prophylactic surfactant is no longer recommended (Grade A).

- Non-invasive respiratory support (e.g., CPAP) should be provided to preterm infants with respiratory distress syndrome (RDS) from birth. Early surfactant should be provided for newborns with increasing severity of RDS, demonstrated by escalating or sustained levels of oxygen requirement and other clinical or radiological indications (Grade B).

- Infants with RDS whose oxygen requirements exceed FiO2 of 0.5 should receive surfactant replacement therapy (Grade A).

- For spontaneously breathing infants on CPAP with RDS, non-invasive methods of surfactant administration, such as LISA or MIST, are preferable. Factors such as clinician experience, optimal dosage, volume, and the types of surfactant available must be considered to optimize delivery method (Grade B).

Canadian Paediatric Society, Fetus and Newborn Committee. Guidelines for surfactant replacement therapy in neonates. Paediatr Child Health 2021 26(1):35-41.