
EXOGENOUS SURFACTANT THERAPY

- Types of exogenous surfactant
 - Genetically engineered human surfactant (genes for protein identified) - future
 - Human - amniotic fluid (HIV ?)
 - Bovine lung (adult cow, calf) - antigenic foreign protein ?
 - » Cow: Survanta
 - ◆ 4 ml/kg/dose every 4-6 hours, up to four doses
 - ◆ SP-B, C surfactant protein
 - ◆ Store refrigerated but let sit at room temperature 20 minutes before use
 - » Calf: Infasurf
 - Porcine: Curosurf - antigenic foreign protein?
 - Synthetic (Exosurf™)
 - » 5 ml/kg/dose every 12 hours, up to four doses
 - » Lack of infectious risks
 - » No foreign protein
 - » Ease of manufacturing
 - » Room temperature storage
 - » Readily usable (e.g., no vortexing prior to use)

- Proposed mechanism of action
 - Stabilization of ventilated terminal airways
 - Recruitment of previously closed terminal airways/alveoli

in functional residual capacity

PaO₂, SaO₂; compliance (?)
 - Reduces edema
 - Antibacterial activity (?)

- Administration of exogenous surfactant
 - Time
 - » Prophylactic - delivery room (≤26 weeks probably beneficial; 27-29 weeks ? benefit; immature L/S ratio ?)
 - » Rescue - first 3-6 hours preferred, up to 24 hours (27-29 weeks, ≥30 weeks) with established RDS
 - » Retreatment - usually need 3-4 doses
 - Dosage
 - » 60-120 mg surfactant per dose
 - » 67.5 mg/kg dipalmitoylphosphatidylcholine (DPPC) - Exosurf
 - Route - intratracheal
 - Guidelines for mechanical ventilation during instillation—no interruption
 - » Maintain PEEP to prevent alveolar closure and facilitate surfactant distribution
 - » May need to increase P-max (PIP) to maintain chest wall motion

- » Reduce P-max after instillation in response to chest wall motion, air entry, PaCO₂
- » Reduce FIO₂ in response to SaO₂, PaO₂ levels

➤ Beneficial effects of exogenous surfactant administration

- *Reduced mortality from RDS
- *Reduced air leak incidence
- †Improved pulmonary compliance (probable)
- †Reduced supplemental oxygen requirements
- †Improved a/A ratio, A-aDO₂ - reduced RDS severity
- †Reduced ventilatory requirements
- Improved x-ray appearance (?)
- Reduced number of NICU days, ancillary charges ?
- Reduced incidence of bronchopulmonary dysplasia - ? (reduced severity probable)
- Reduced incidence of intraventricular hemorrhage - ?
- Reduced cardiopulmonary destruction ?

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 * significant effects
 † improved pulmonary status

➤ Summary of clinical replacement studies (bovine, porcine, synthetic)

	Prophylactic Studies		Rescue Studies	
	Surfactant	Control	Surfactant	Control
Mortality*	12.3%	25.0%	by 50.0%	15-30%
Pneumothorax*	11.4%	29.0%	8.4%	44.0%
PIE*	5.7%	43.5%	6.5%	35.0%
BPD	30.8%	37.3%	19.6%	29.0%
NEC	7.5%	10.3%	7.0%	6.8%
IVH	21.2%	31.3%	30.8%	47.0%
PDA	34.9%	32.0%	59.8%	46.0%
*p ≤ 0.05				

➤ Summary of clinical studies (synthetic, cow, porcine, calf, human)

	Surfactant Therapy*			
	Prophylactic [†]		Rescue	
	Natural	Synthetic	Natural	Synthetic
RDS Incidence	↓	↓	—	—
RDS Mortality	↓↓↓	↓↓↓	↓↓↓	↓↓
BPD/Mortality	↓↓	↓	↓↓	↓↓↓
Air Leak	↓↓↓↓	↓↓↓	↓↓↓↓	↓↓↓
RDS Severity				
FIO ₂	↓↓	↓	↓↓↓ (Curosurf ↓↓↓↓↓)	↓ (Slower)

Ventilatory Requirements	↓↓	↓	↓↓ (Curosurf ↓↓↓)	↓ (Slower)

PDA	↑ (?)	↑	—	↓(?)
IVH	—	—	—	↓(?)
BPD	—	? ↓ severity	—	↓(?)
*Summary of randomized, controlled studies <30-32 weeks gestation				
†≤26 weeks; over 40% of infants 29-32 weeks gestation may not require surfactant				

- Side effects of exogenous surfactant therapy NOT observed in majority of studies
 - Worsening of mild RDS or wet lung syndrome
 - Patent ductus arteriosus (?)
 - Necrotizing enterocolitis
 - Intraventricular hemorrhage
 - Retinopathy of prematurity
 - Sepsis/pneumonia (Survanta -?)
 - Antigen production (cow / calf / porcine lung)

- Side effects of exogenous surfactant therapy observed in studies
 - Apnea (earlier discontinuation of ventilatory support)
 - Endotracheal tube obstruction
 - Pulmonary hemorrhage [extremely low birth weight infants, ≤750 grams; Exosurf, Survanta (?)]

- Questions regarding exogenous surfactant administration
 - Effectiveness of rescue vs. prophylactic therapy - role of gestational age, age at administration
 - Effect of prenatal steroids - additive effect

	Steroids		No Steroids	
	Surfactant (n=57)	No Surfactant (n=46)	Surfactant (n=555)	No Surfactant (n=566)
Mortality from RDS (%)	0*	7*	7*†	20*†
BPD (%)	49	55	61	62
Air leak (%)	2*	13*	11†*	23†
PDA (%)	28‡	22‡	47‡	44‡
IVH (III, IV) (%)	7†	11	25†	23
	† p<0.001		* p≤0.05	
			‡ p<0.005	

Jobe AH, et al. Am J Obstet Gynecol 168:508, 1993

- Optimal dosage, treatment intervals, number of treatments (length of response in patients)
 - » Lack of response in certain patients
 - » Structural immaturity
 - » Infection
 - » Inhibitors
 - ◆ Pulmonary edema (PDA)
 - ◆ Rapid metabolism
 - ◆ Ventilatory support
- Effectiveness in lungs with secondary deficiency of surfactant?
- Effectiveness in other disorders?

- » Meconium aspiration likely (repeated doses necessary)
 - » Diaphragmatic hernia
 - » Pneumonia
 - » ARDS
 - Interaction with endogenous surfactant if mild or no RDS
 - Long-term toxicity - ?
- Surfactant administration
- Surfactant administration is performed by trained physicians, nurses and respiratory therapists
 - » Start with resuscitation and stabilization of preterm infant
 - Necessary equipment to support premature infants on site and available to use by trained physicians and health care professionals, including
 - » Bag, mask, laryngoscope, endotracheal tube, oxygen
 - » Positive-pressure ventilation
 - » Radiologic services
 - » Laboratory services
 - Approved surfactant therapy protocol (see attached)

Surfactant is not a substitute for transfer / transport of high-risk pregnant women, when indicated, nor for intensive care therapy

From American Academy of Pediatrics 87:946, 1991

SURFACTANT ADMINISTRATION PROTOCOL

- How supplied
- Survanta (beractant) intratracheal suspension is supplied in a glass vial containing 8 ml
- Dosage
- The dosage of Survanta is 4 ml/kg every 6 hours for four doses
 - This dose should be given no more frequently than every 6 hours
 - This dose is usually given four times, unless it becomes contraindicated or if not needed ($FIO_2 < 0.3$)
- Suggested equipment for administration
- Ambu bag
 - Oxygen source
 - 5 French feeding tube
 - Syringe and 20-gauge needle
 - Measuring tape (optional)
 - Sterile scissors

- Endotracheal tube (proper size and length)
- Laryngoscope (0 or 1 blade)

➤ Preparations

- Survanta should be inspected visually for discoloration prior to administration
- The color of Survanta should be off-white to light brown
- If settling occurs, swirl the vial gently — **DO NOT SHAKE**
Survanta is to be stored refrigerated
- Survanta should be warmed at room temperature for at least **20 minutes** or warmed in the hand for at least 8 minutes — artificial warming should **NOT BE DONE**
- Unopened, unused vials may be returned one time to the refrigerator and stored, even after having been warmed, if less than 8 hours have elapsed since warming

➤ Administration

- Using the syringe and the needle, draw the Survanta up slowly
- Do not use a filter needle
- If desired, you may want to clip the end of the feeding tube so the tip will reach just to the end of the endotracheal tube when inserted
 - » The syringe can then be connected to the shortened feeding tube
 - » Cutting the feeding tube makes it easier to handle and ensures that the Survanta will be instilled at the tip of the endotracheal tube
- After proper endotracheal tube placement has been confirmed on a chest x-ray (if possible in the delivery room), the infant should be suctioned prior to administration
 - » Once the Survanta has been given, the infant should not be suctioned for at least 2 hours unless clinically needed
- Place the infant in four different positions (see below) during administration of Survanta
 - » While the infant is in each position, one-quarter dose of the Survanta will be administered intratracheally via the 5 French feeding tube
 - » After each administration, the infant should be ventilated (may need a higher pressure for chest wall excursion) using an FIO₂ of at least 0.2 higher than baseline, or as needed, until the oxygen saturation (SaO₂) level is above 90% and the heart rate returns to normal
- Positions
 - » The first one-quarter dose should be administered with the infant in the **Trendelenburg** position, head to the right, and the infant tilted slightly to the right

- » The second one-quarter dose should be administered with the infant in the **Trendelenburg** position, head to the left, and the infant tilted slightly to the left
- » The third one-quarter dose should be administered with the head **elevated** and turned to the right, with the infant's body tilted to the right
- » The last one-quarter dose should be administered with the infant's head **elevated** and turned to the left, with the infant's body tilted to the left

SURVANTA PRECAUTIONS

- Survanta should be administered, or supervised, by clinicians experienced in intubation and ventilator management of infants.
- Surfactant is not always effective, and is not viewed as therapy to decrease high-risk maternal referrals.
- Systemic oxygenation (PaO₂, SaO₂) and ventilation (PaCO₂) need to be closely monitored after administration to avoid hyperoxia and hypercarbia with risk for pneumothorax.
- Acute airway obstruction can result from blockage of the endotracheal tube with Survanta.
- Obstruction usually results from large doses, delivery of the dose high up in the endotracheal tube, or small diameter endotracheal tube (e.g., 2.5 mm).
- Hand/bag ventilate with sufficient O₂ to prevent cyanosis, and sufficient positive pressure to provide adequate air exchange and chest rise during initial administration of Survanta.
- Manufacturer recommends against hand/bag ventilation during repeat dosing.
- The recommendation is a ventilation rate of 30 breaths per minute or greater, with an inspiratory time of less than one second and an FIO₂ of 0.2 greater than baseline—or sufficient to prevent cyanosis.
- Clinical assessment of adequate chest rise, heart rate and oxygenation is essential to maintain appropriate ventilation.
- If the infant experiences bradycardia or desaturation during dosing, stop and initiate appropriate measures (increase pressure, oxygen) to correct the situation until the infant is stabilized, then resume dosing.
- Delivery of Survanta with the feeding tube past the end of the endotracheal tube, or without assessment of endotracheal tube position above the carina, can result in unequal distribution of Survanta—which may adversely affect ventilation.

- Infants with poor compliance and/or having an endotracheal tube with a large air leak may “reflux” Survanta through the nose and mouth.
- Ideally, reintubation should be done with a larger tube.
- If reintubation is not possible, first administer Survanta in the head-up position and apply cricoid pressure in the Trendelenburg position.
- Redose every six hours if the infant remains intubated and requires an FIO₂ of 0.3 or greater to maintain a PaO₂ ≤80 torr.

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