



# Surfactant Delivery in Neonatal Intensive Care

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I do intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.



# Objectives

What is surfactant?

Why is surfactant important?

What are the available methods of delivering surfactant?

Describe the benefits of using less invasive surfactant administration



# Surfactant

# Why do we need surfactant?

- Respiratory distress syndrome (RDS) is the most common cause of respiratory failure in newborns born prematurely.
- Prior to exogenous surfactant therapy, thousands of preterm infants died of RDS each year.
- Incidence RDS is inversely proportional to gestational age
  - 60% of infants born <28weeks
  - 30% of infants born 28 – 34 weeks
  - <5% of infants born after 34 weeks



# Discovery of Surfactant

- Kurt von Neergard began work on understanding the role surface tension plays in neonatal lung
- Peter Gruenwald also discovered importance of surface tension in work of breathing
- 3 scientists working separately with nerve gas discovered a substance on lining of lungs that reduced surface tension
  - John Clements in US

**1929**

  
**Kurt von Neergard**  
1887-1947

– Surface tension as a force counteracting the first breath of the newly born baby should be investigated further

**1947**

**Peter Gruenwald**

– Resistance to aeration is due to surface tension. No idea about von Neergard's experiments

**1950s**

Canada	England	USA
 <b>Charles Macklin</b> 1883-1959	 <b>Richard Pattle</b> 1918 - 1980	 <b>John Clements</b> 1923 -

**Effects of nerve gases on lungs**

Bubbles covered by a substance from the lining layers in the lung

Halliday, *J of Paediatrics and Child Health*, 2017.

# Discovery of Surfactant

- Dr Mary Ellen Avery discovery of the link between surface tension, hyaline membrane disease (RDS) and surfactant
- Mortality rate of prematurely born infants with RDS was over 90% in the pre- surfactant days
- Death of Patrick Bouvier Kennedy in 1963 sparked a race to save prematurely born infants dying from respiratory failure

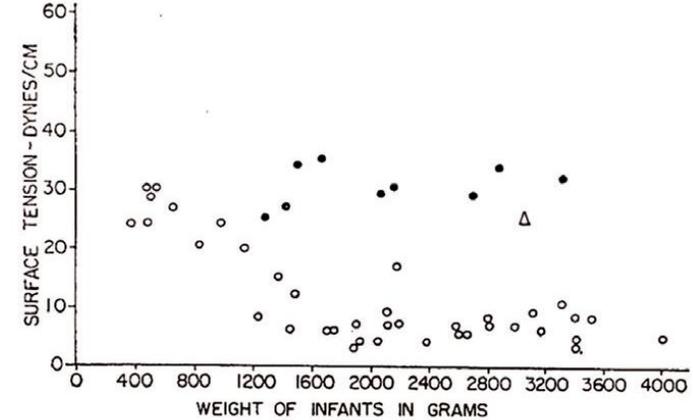


Fig. 3.—Lowest surface tension measured on compression of the surface. Open circles=infants dying from causes other than hyaline membrane disease. Closed circles=infants dying with hyaline membrane disease. Triangle=stillborn infant of a diabetic mother.



Mary Avery

1927 - 2011

Avery ME, Mead J: Am J Dis Child 1959;97:517-523



# Discovery of Surfactant

- Dr Fujiwara was the first to publish the treatment with a modified natural surfactant in humans (10 premature infants, 8 survived)
- 1980's and 1990s
  - several surfactant development, dosing trials
  - late rescue treatment (unlike today)
  - mortality reduced to 30% with single dose treatment and 10% with multiple doses

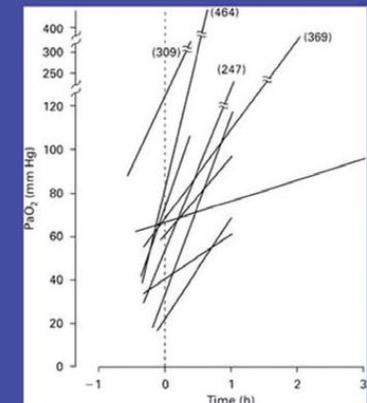


**Tetsuro Fujiwara**

1931 –

- Surfactant TA
- 10 infants
- 30 wk; >1500 g
- 9 had PDA
- 2 died

1. Worked in Adams' laboratory in Los Angeles, California in the 1960s and the 1970s
2. Returned to Japan and treated ten preterm babies with a modified natural surfactant (Surfactant-TA)

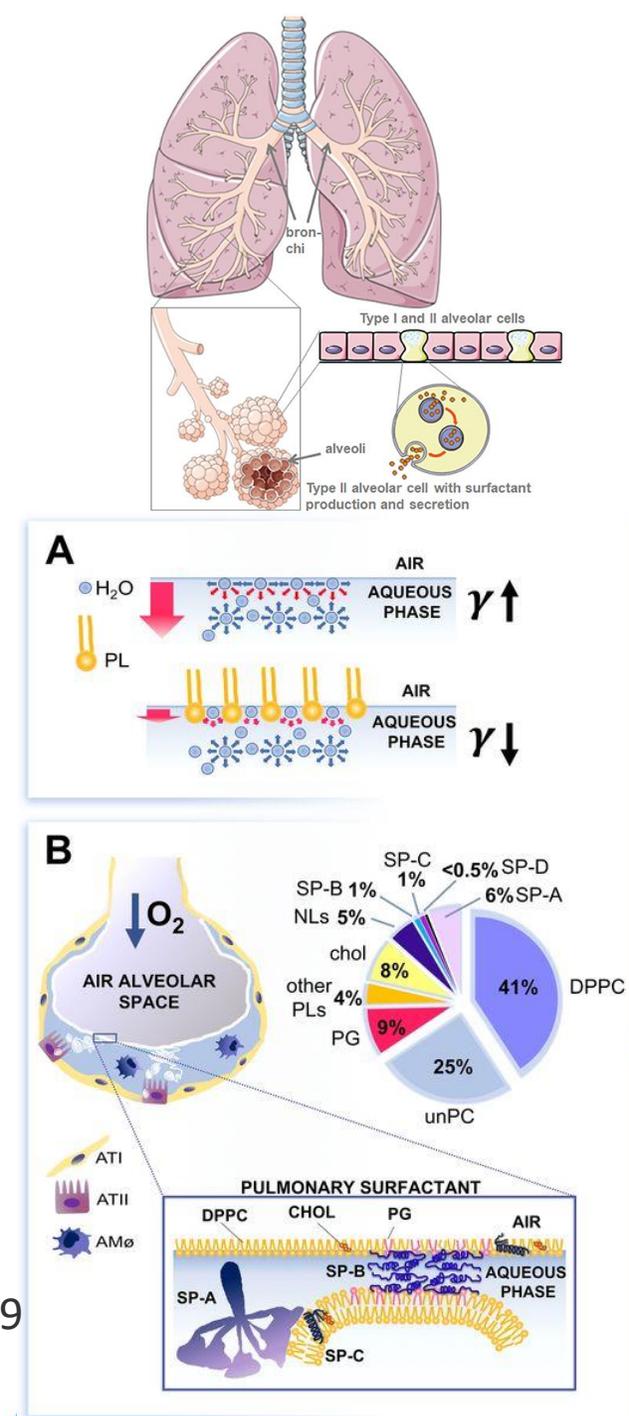


**Fujiwara et al: Lancet 1980; i:55-59**

Halliday, *J of Paediatrics and Child Health*, 2017

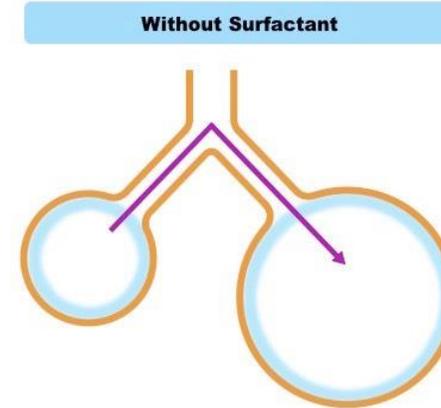
# What is Surfactant?

- Surfactant is produced and secreted by type II pneumocyte cells in the alveoli
- It is a complex mixture of lipids (90%) and proteins (10%)
- Disaturated Dipalmitoyl phosphatidylcholine (DPPC) 70% + unsaturated phosphatidylcholine (PC) 25% + anionic phosphatidylglycerol (PG) + smaller fractions of other phospholipids.
- The surfactant proteins include SP-A, SP-B, SP-C, SP-D.



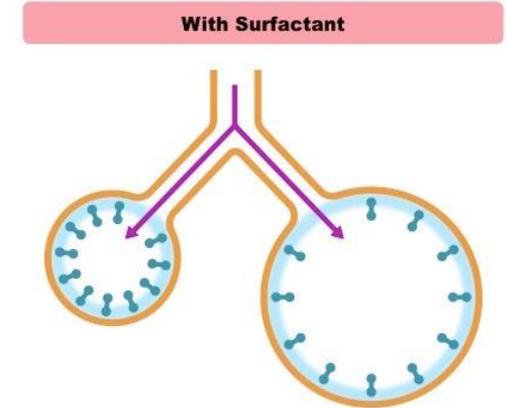
# Surface Tension

- The alveoli have water molecules coating the inner lining, and gas in the middle
- Water exhibits significant surface tension due to the intermolecular hydrogen bonding between water molecules. This pressure (P) causes alveoli to collapse inward (atelectasis) making gas exchange very difficult.
- The magnitude of the inward collapsing pressure is determined by Law of Laplace  $P = 2T/r$
- Surfactant reduces surface tension (T). As alveoli become smaller (r), surfactant molecules are squeezed together increasing their concentration, which reduces surface tension even more.



Alveoli **1** and **2** have equal surface tension  
**1** has higher pressure (due to smaller radius)  
**1** more likely to collapse and be harder to inflate

$r = 1$	$r = 2$
$T = 3$	$T = 3$
$P = 2 \cdot 3 / 1$	$P = 2 \cdot 3 / 2$
$P = 6$	$P = 3$



**1** has less surface tension (more surfactant per area)  
**1** and **2** have equal pressure (due to surfactant)  
**1** will inflate at a faster rate than **2** (until equal in size)

$r = 1$	$r = 2$
$T = 1$	$T = 2$
$P = 2 \cdot 1 / 1$	$P = 2 \cdot 2 / 2$
$P = 2$	$P = 2$

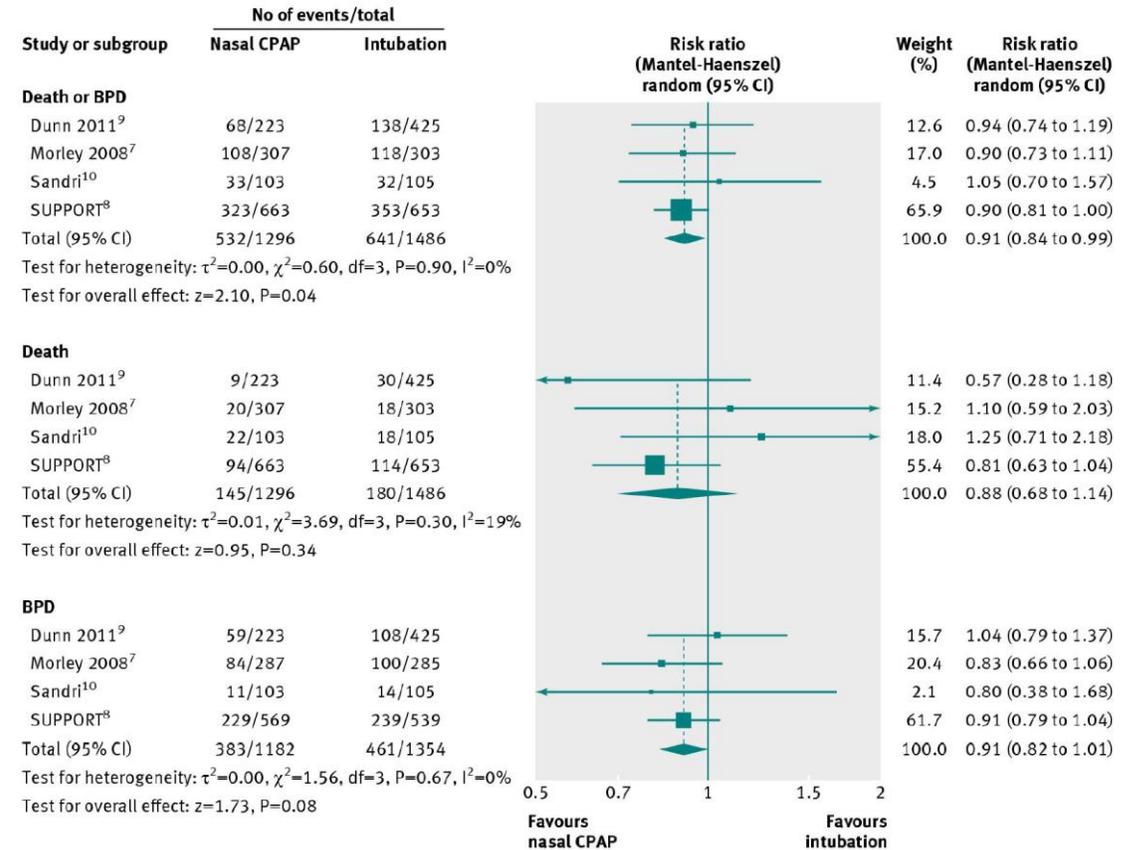
BioNinja

# Surfactant Preparations: Which is best?

- Since the 1980s there have been many attempts at harvesting or developing the optimal surfactant preparation for the treatment of neonates with RDS.
- The animal derived surfactants are well studied and equally effective overall, despite slight differences in the origin (bovine vs porcine), method of processing (minced lung extract vs lung lavage) and protein content.
- Direct comparison trials are complicated by differences in indications for dosing (rescue, prophylactic, initial doses). When adjusting for these factors, the differences among the surfactant formulations result in very similar major outcomes of RDS, death, pneumothorax.

# Timing of Surfactant Delivery

- Although surfactant dosing has proven to **reduce mortality** and **pneumothorax**, and other complications, the timing of dosing in relation to other interventions in the care of preterm infants has evolved over the last 3 decades.
- Initial stabilization of very preterm infants with **continuous positive airway pressure (CPAP)** rather than with routine intubation and surfactant administration to prevent RDS immediately after delivery is an optimal approach.

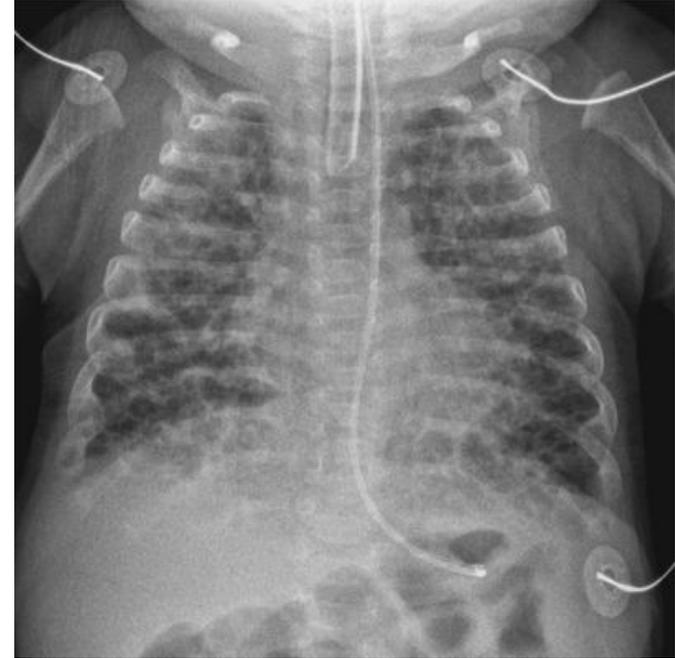


# Surfactant Administration



# Methods of Surfactant Administration

- The main challenge with the care of premature infants in the 1980s was to reduce death from early lung injury (air leaks, pneumothorax)
- Although surfactant dramatically improved this, many survivors were left with lung injury from prolonged mechanical ventilation.
- The standard method of dosing/delivery of surfactant was to endotracheally intubate, provide positive pressure ventilation, obtain radiographs to confirm ETT position, instill surfactant within the first hours of life, wean ventilatory support to eventual trial of extubation.
- Some thoughtful clinicians looked to develop other methods of delivering surfactant into the trachea without keeping baby on ventilator, as prolonged mechanical ventilation worsens lung injury of a preterm infant.



*Radiology Key*

# Methods of Delivery: InSurE

- Babies needed PEEP to maintain FRC
- Intubate, dose surfactant via ETT, extubate to nasal CPAP.
- The practice was not standardized
- Variation in timing of ETT removal resulted in mixed outcomes
- INSURE is effective in delivering surfactant safely and led to earlier extubation than standard method.

  
**IN**tubation

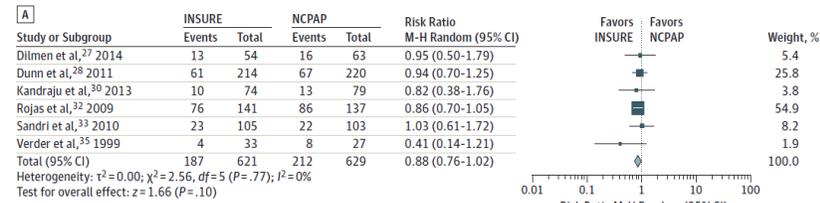
  
**SUR**factant

  
Rapid **E**xtubation  
*Curosurf*

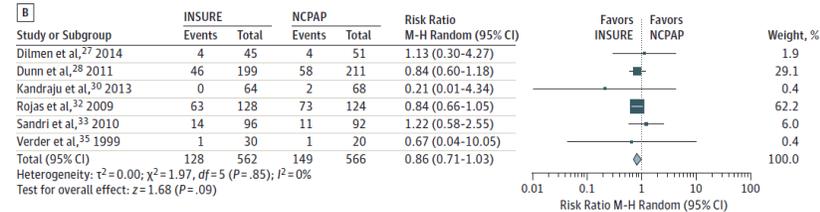


# INSURE vs CPAP

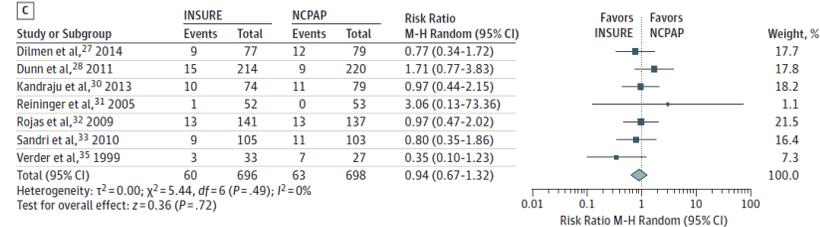
- Multiple small studies revealed improved short-term outcomes
- Systematic review and meta-analysis of several major trials revealed **no difference** between INSURE and CPAP in 5 main outcomes



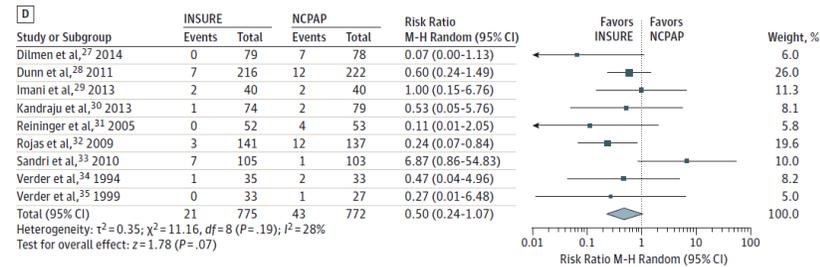
BPD and/or death



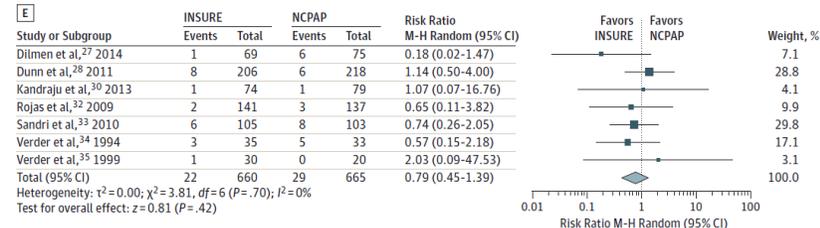
BPD alone



Death alone



Air leak



Severe IVH

# INSURE

- Historical: Intubation, surfactant, mechanical ventilation
- Recent Past: Intubation, surfactant using ET tube, extubation following a short period of ventilation (PPV or mech ventilation).
- Potential risks
  - Laryngoscopy with endotracheal intubation can result in larynx or tracheal injury
  - Utilizing medications for sedation and analgesia during intubation can have side effects
  - Maintaining a preterm infant on mechanical ventilation with positive pressure, even for short period of time, can cause lung injury and lead to BPD



# Modifications of INSURE

- Some clinicians began to look at other ways to modify the INSURE method utilizing thin catheter administration of surfactant.
- Visualizing airway with laryngoscopy, inserting very **thin catheter** into trachea to delivery surfactant while patient continues on NCPAP support
- Avoiding the use of standard sized ETT, or PPV/mechanical ventilation
- Advantage:
  - Smaller tube/catheter is less traumatic
  - Patient is breathing spontaneously with NCPAP support (no mechanical or PPV breaths)



# Less Invasive Surfactant Administration

# Less Invasive Surfactant Administration Methods

**Table 1.** Published methods to combine continuous positive airway pressure, spontaneous breathing and surfactant administration

Name	Device type	Procedure/instruments	Reference
Cologne method	Flexible suction catheter	Laryngoscope + Magill forceps	Kribs <i>et al.</i> [6]
SONSURE	Flexible nasogastric tube	Laryngoscope + Magill forceps	Aguar <i>et al.</i> [26]
Take Care method	Flexible nasogastric tube	Laryngoscope, no forceps	Kanmaz <i>et al.</i> [15]
Hobart method	Semi-rigid vascular catheter Device name: for example, Lisacath	Laryngoscope, no forceps	Dargaville <i>et al.</i> [27]
QuickSF	Soft catheter Device name: Neofact	Laryngoscope + intrapharyngeal guidance device	Maiwald <i>et al.</i> [28]
INSURE	Endotracheal tube	Laryngoscope	Verder <i>et al.</i> [3]
Laryngeal Mask method	Special device placed in hypopharynx	No Laryngoscope, no forceps	Roberts <i>et al.</i> [29 <sup>a</sup> ]
Aerosol method	No catheter Nebuliser with, for example, mask/prongues	No Laryngoscope, no forceps	Pillow <i>et al.</i> [30]
Pharyngeal Surfactant	Flexible short tube and syringe Injection into the pharynx	No Laryngoscope, no forceps	Kattwinkel <i>et al.</i> [31]



# German RCT LISA vs Conventional in ELBW

Outcome	Intervention (n=107)	Control (n=104)	p value
Survival without major complication	54 (50.5)	37 (35.6)	0.02
<b>Mechanical Ventilation</b>			
All Infants	80 (74.8)	103 (99.0)	<0.001
GA 23 wks	14/15 (93.3)	9/9 (100)	>0.99
GA 24 wks	24/26 (92.3)	30/31 (96.8)	0.59
GA 25 wks	24/31 (77.4)	41/41 (100)	0.002
GA 26 wks	18/35 (51.4)	23/23 (100)	<0.001
Duration of Mechanical Ventilation (median (IQR))			
All infants	5 (0-17)	7 (2.5-19.5)	0.031
Grade 3 or 4 IVH	11 (10.3)	23 (22.1)	0.02

# Large RCT of ELBW Infants: OPTIMIST-A Trial

Dargaville, et al. *JAMA* 2021

- 33 tertiary-level neonatal intensive care units in Australia, Canada, Israel, New Zealand, Qatar, Singapore, Slovenia, the Netherlands, Turkey, the UK, and the US
- 25 0/7 to 28 6/7wks gestation, spontaneously breathing on CPAP or NIPPV with  $FiO_2 > 0.3$  in first 6hrs of life
- Study group received MIST (Hobart method with thin angiocatheter) vs control (Sham treatment, simple repositioning)
- Strict intubation criteria for respiratory failure
- Primary outcome composite of death before 36weeks or BPD
- Secondary outcomes: pneumothorax, severe IVH, cystic PVL, severe ROP and other commonly reported preterm outcomes

Effect of Minimally Invasive Surfactant Therapy vs Sham Treatment on Death or Bronchopulmonary Dysplasia in Preterm Infants With Respiratory Distress Syndrome  
The OPTIMIST-A Randomized Clinical Trial

Dargaville, et al. *JAMA* 2021

- 488 infants were randomized, 242 to MIST and 244 to control
- Mean gestational age at birth of 27.3 weeks' and a birth weight of approximately 930 grams
- Result: No statistically significant difference in the primary outcome was found between groups. Death or bronchopulmonary dysplasia assessed at 36 weeks' PMA occurred in 105 infants (43.6%) in the MIST group and in 121 infants (49.6%) in the control group.
- Secondary outcomes favored MIST:
  - the need for intubation within 72 hours of birth
  - pneumothorax requiring drainage
  - intubation at any time
  - incidence of patent ductus arteriosus requiring medical therapy
  - need for oxygen therapy at home in survivors to hospital discharge
  - duration of mechanical ventilation, CPAP, and all forms of respiratory support

# OPTIMIST-A Trial

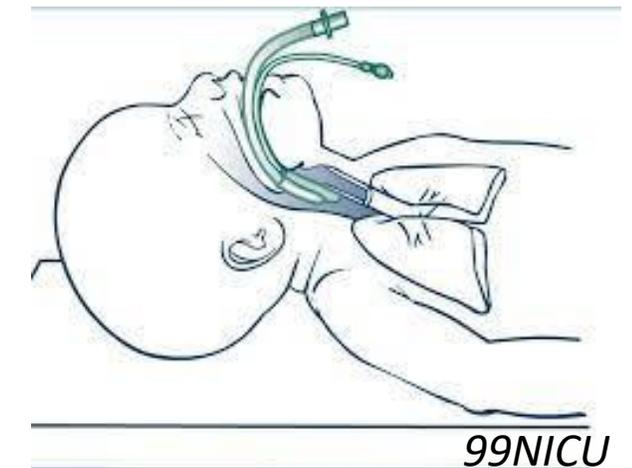
- Despite a significant decrease in MV exposure, there was no statistically significant difference in the primary outcome (death or BPD)
- Importantly, a subgroup analysis revealed interaction between GA and death (favoring control at lower GA) and exposure to mechanical ventilation (favoring MIST to a greater extent at higher GA)
- These data are indispensable as they inform the effect of early rescue MIST in the most relevant target population (<28 wks) and compared to the current standard of care (CPAP)
- These data encourage stratification of infants <28 wks GA. In this study, MIST had a greater reduction in MV at <72 hours in the 27-28 wk stratum (higher gestational age)



# Lesser Invasive Methods

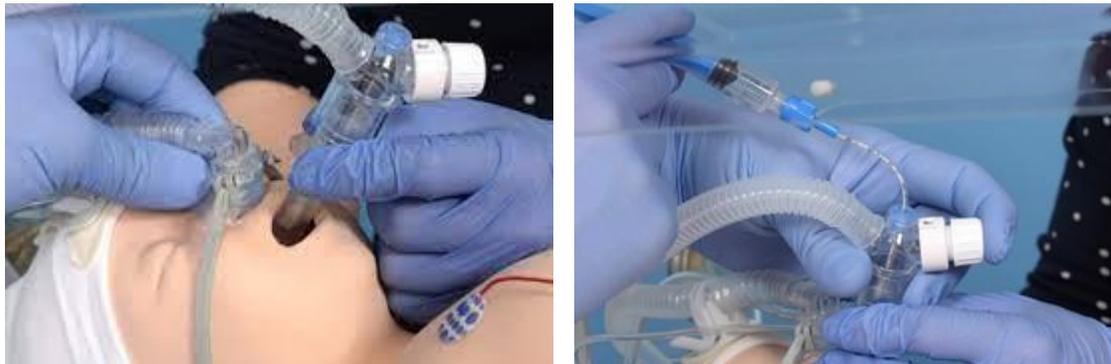
# Surfactant Delivery by Laryngeal Mask Airway

- Surfactant Administration through Laryngeal or Supraglottic Airway (The SALSA) method
- Consists of inserting a supraglottic airway device (LMA), into the mouth and advancing until device can't be advanced further.
- Proper placement is indicated by listening for bilateral breath sounds and color change on a carbon dioxide detector
- A piece of tubing connected to the surfactant syringe is then placed into the lumen of the device to deliver the surfactant in aliquots just above the vocal cords
- Advantage over other methods is insertion of the device through the vocal cords, therefore, use of a laryngoscope is not required for proper placement of the device.
- Insertion of the LMA is substantially easier and faster than the insertion of an ETT, and decreases the risk of trauma to the glottic and subglottic tissues



# SALSA

- Supraglottic airway devices for surfactant treatment: systematic review and meta-analysis Calevo, et al. *J. Perinatology*, 2019
- **Objective:** To compare surfactant administration via supraglottic airway device (SAD) vs. nasal CPAP alone or INSURE.
- **Conclusions:** In preterm infants with RDS, surfactant administration via SAD reduces the need for intubation/mechanical ventilation. Overall, available literature includes few, small, poor-quality studies. Surfactant administration via SAD should be limited to clinical trials.



NHSGGC



# Aerosolized (Nebulized) Surfactant

- Surfactant that is formulated in small particles to be delivered in aerosolized form to premature babies
- The goal of aerosolizing surfactant has been in development for over 30 years, but has been met with many production challenges and lack of efficacy in small trials
- Large multicentered RCT (AERO 2 Study) from 22 NICUs, and 457 infants 23-41wks (mean 33 weeks) assessed the efficacy of aerosolized surfactant in preterm infants with RDS on noninvasive respiratory support.

Cummings, et al. *Pediatrics*, 2020

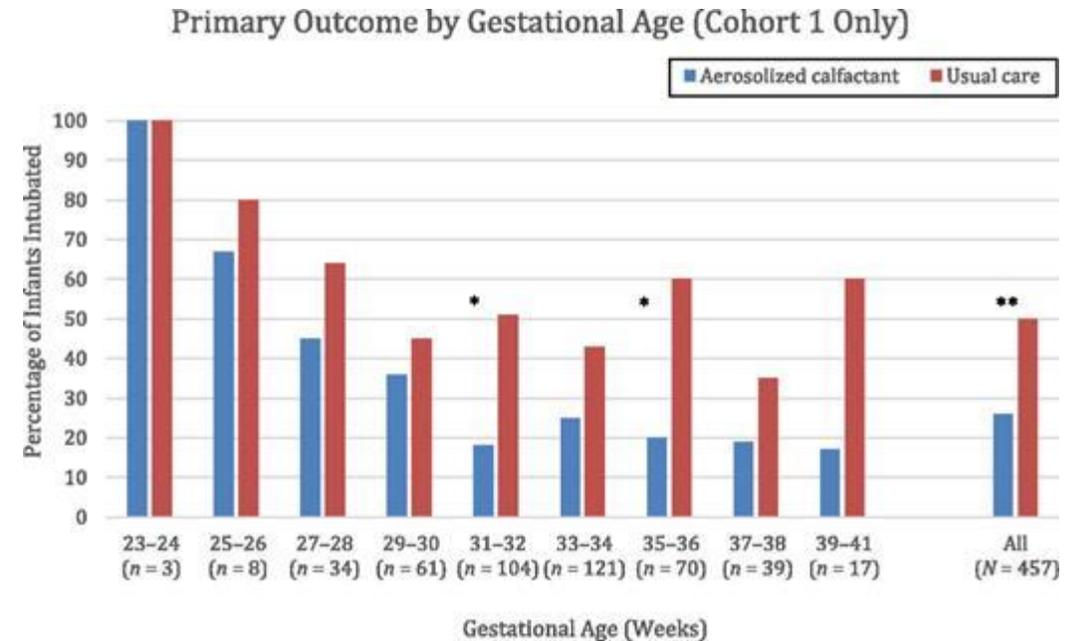


# Aerosolized Surfactant

- Calfactant was aerosolized by using a Solarys nebulizer modified with a pacifier adapter; 6 mL/kg were delivered directly into the mouth. Infants in the aerosol group received up to 3 treatments, at least 4 hours apart.
- Infants in the control group received usual care, determined by providers. Infants were intubated and given instilled surfactant for persistent or worsening respiratory distress, at their providers' discretion.
- The rates of intubation for surfactant instillation were 26% in the aerosol group and 50% in the usual care group ( $P < .0001$ ). Respiratory outcomes up to 28 days of age were no different.

## Conclusions:

- In newborns with early, mild to moderate respiratory distress, aerosolized calfactant reduced intubation and surfactant instillation by nearly one-half.



Cummings, et al. *Pediatrics*, 2020

## Cautions:

- Mean 33 wks, 2.1kg. Babies <27wks ( $n=11$ )
- Rate of surfactant use for 33wk babies was very high compared to other large studies
- Intervention group required higher doses (6ml/kg) and multiple doses (upto 3 doses)
- No difference long term (BPD, death)

# Summary

- Surfactant is a complex mixture of lipids (mostly) and proteins that lowers surface tension in the lungs.
- The main therapy for preterm infants with RDS is maintaining end expiratory pressure with CPAP. Targeted use of surfactant is highly effective.
- In infants who do not require placement of endotracheal tube for respiratory support, delivery of surfactant via less invasive administration is the optimal mode of delivery, over INSURE.
- Newer less invasive methods of surfactant delivery are being studied but need more evaluation to assess for effectiveness and optimal outcomes



# Surfactant Delivery in the Neonatal Intensive Care Unit

Irma Reyburn, RCP

Kathy McAliester, RCP

Jami Vaca, RN



**MemorialCare**<sup>TM</sup>  
Miller Children's & Women's  
Hospital Long Beach

# LISA Pre-Procedure Preparation

- Documentation
- Supplies
- Team Roles
- Positioning
- Vitals





# Supplies

- 16g Angiocath
- T-Connector
- 5ml Syringe
- Tape Measure
- Tape
- Video Laryngoscope
- Curosurf® surfactant





# Team Roles

## **Physician**

Stands at head of the patient

Laryngoscopy and catheter insertion

## **Respiratory Care Practitioner**

Stands at the head of the patient

Maintains Bubble CPAP

Delivers Surfactant

## **Registered Nurse**

Stands at the foot of the patient

Provides comfort positioning while maintaining infant in midline position, careful to avoid applying pressure on the chest



# Pre-Procedure



- RCP measures and marks the angiocath with depth of insertion
- Removes and disposes of needle appropriately
- Ensures Curosurf® is at appropriate temperature
- Prepares and confirms functionality of video laryngoscope/laryngoscope
- RN/RCP removes the chin strap
- Ensure infant's SpO2 is WNL
- Position infant supine in midline position
- Ensure adequate BCPAP is maintained throughout the procedure

# Pre-Procedure Vitals

26 Weeks Gestational Age

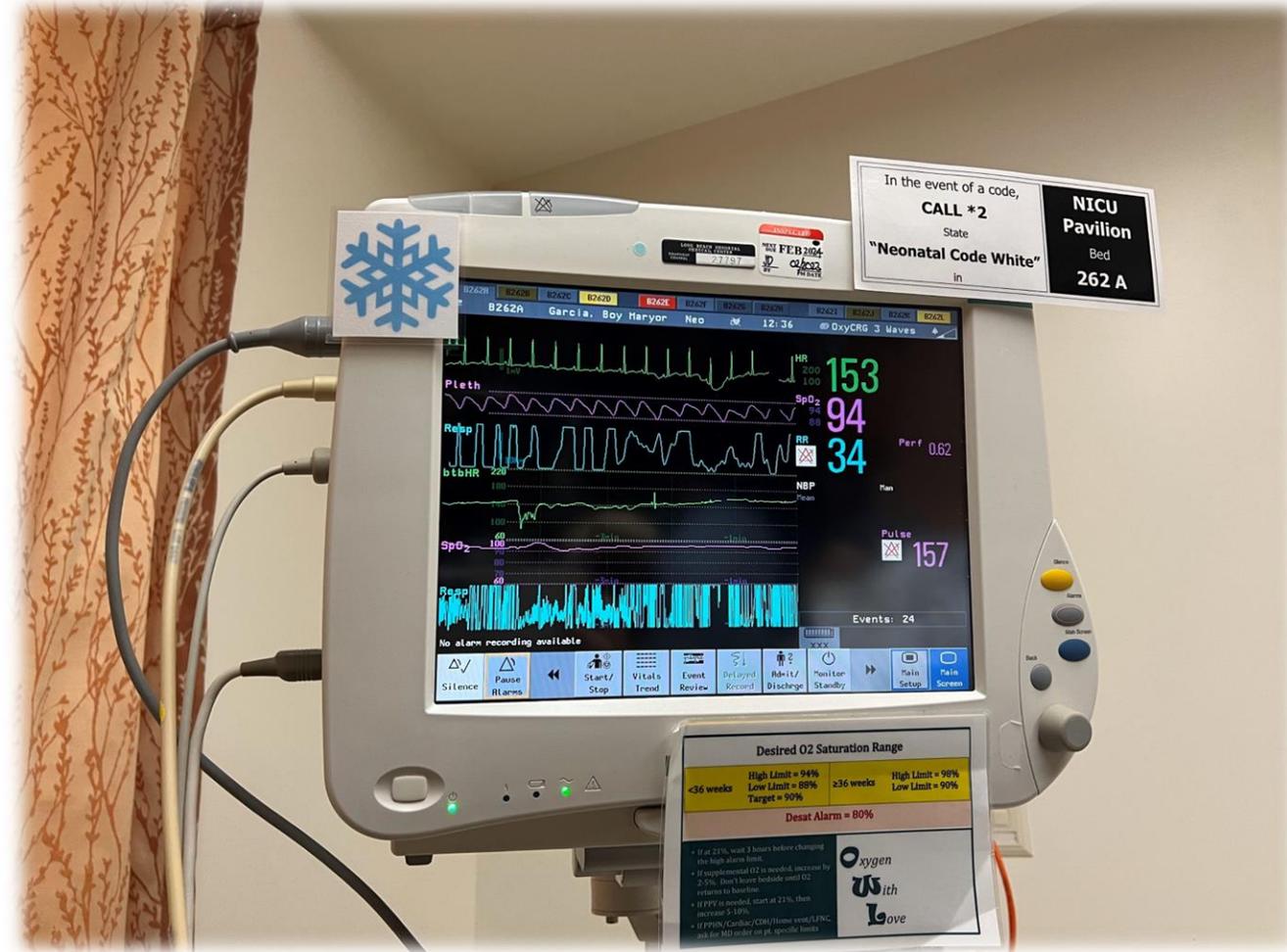
680 grams

Bubble CPAP +6

FiO2 0.4

SpO2 94%

12:36pm



# Surfactant Delivery

# Post Procedure Vitals

26 Weeks Gestational Age

680 grams

Bubble CPAP +6

FiO2 0.22

SpO2 100%

12:47pm





Thank You

Antoine Soliman, M.D.  
Irma Reyburn, RCP  
Kathy McAliester, RCP  
Jami Vaca, RN



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