Alternative Modes of Surfactant Replacement Therapy

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Disclaimer

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Current Trends in the NICU

- General use of antenatal steroids when possible
- Non-invasive modes of respiratory support
  - High Flow Nasal Cannula (HFNC)
  - Nasal Continuous Positive Airway Pressure **(NCPAP)**
  - Non-Invasive Positive Pressure Ventilation (NIPPV)
  - Neurally Adjusted Ventilatory Assist (NAVA)
  - Goal of above is to decrease the rate of Chronic Lung Disease

A Couple of Thoughts on CLD/BPD

- Prematurity
- Positive pressure ventilation

Continuous Positive Airway Pressure "mimics" some surfactant properties[1]

- Increases alveolar stability
- Improves alveolar inflation uniformity
- Separates alveolar gas and liquids at the alveolar surface
- Prevents alveolar collapse
- Decreasing negative pressures needed to open airways
- Decreases the work of breathing (WOB)

Yet the pathophysiology for Respiratory Distress Syndrome remains "surfactant deficiency"

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1. Strang LB. Neonatal Respiration. JB Lippincott Company, Philadelphia, 1977, pp 231-234.

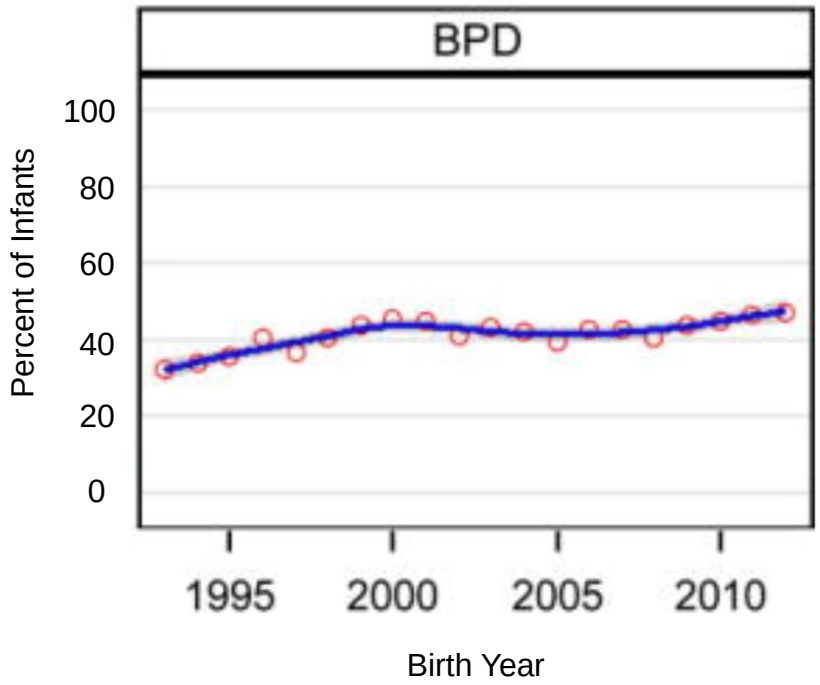
So If We Do Decide to Treat With Surfactant

- Decrease in prophylaxis treatment (first hour of life)
  - Timing for the initial dose remains unclear.
- Practice of “Watch and Wait” before surfactant instillation
  - Not all premature babies will need surfactant. How do we know which ones will?
- Treating RDS versus preventing RDS
  - Increasing respiratory support could mean atelectasis due to surfactant deficiency.
- Have shifts in practice changed outcomes?

Bronchopulmonary Dysplasia (BPD)[1]

Bronchopulmonary Dysplasia (BPD)

Redrawn from Stoll BS, et al. 2015



"Among extremely preterm infants (GA 22-28 weeks) born at US academic centers over the last 20 years, changes in maternal and infant care practices and modest reductions in several morbidities were observed, although bronchopulmonary dysplasia increased." (Stoll, 2015)

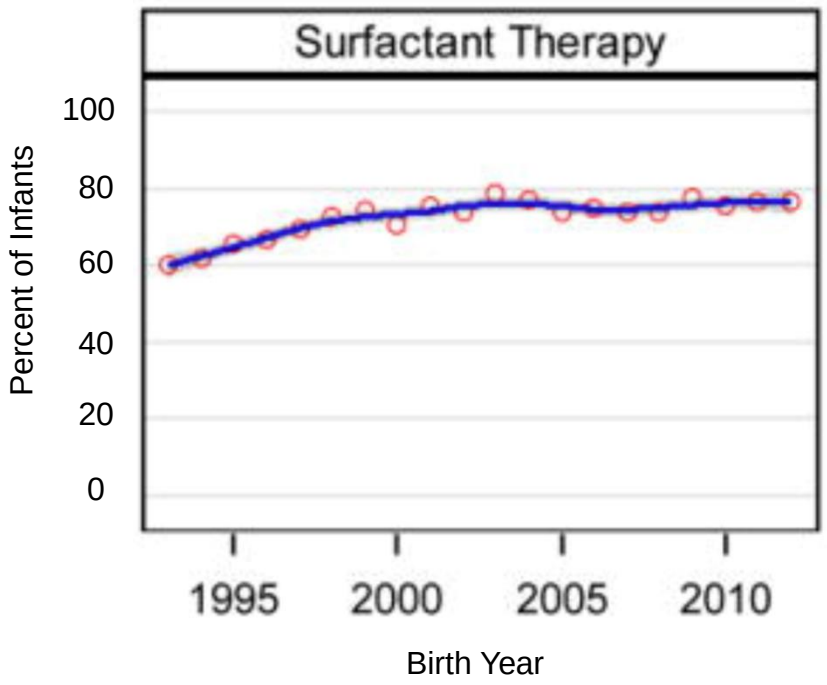
1. Stoll BS, Hensen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates,1993–2012. JAMA. 2015; 314(10): 1039–1051.

Define BPD

- No consistency in defining paramenters

Surfactant Therapy[1]

Surfactant Therapy
Redrawn from Stoll BS, et al. 2015



"Delivery room tracheal intubation, resuscitation drugs, and chest compression decreased over time, while surfactant use increased." (Stoll, 2015)

Surfactant Given[1]

- 1993: 861/1433 (60%)
- 2003: 1501/1913 (78%)
- Increases in all GAs except infants born at 22 weeks.
- After 2003, surfactant use decreased slightly among infants born at 27–28 weeks.

1. Stoll BS, Hensen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates,1993–2012. JAMA. 2015; 314(10): 1039–1051.

Current Methods of Instillation

- **Liquid**
  - Intubation via ETT - **Only FDA approved method for surfactant instillation in USA**
    - InSurE (Intubate, Surfactant, Extubate)
    - In and out surfactant based on clinical assessment

- **MIST** (Minimally Invasive Surfactant Therapy) - **Not FDA approved in USA**
  - LISA (Less Invasive Surfactant Administration) / Thin Catheter Administration (TCA)
    - Catheter or Angio-Cath thru the cords with a slow trickle instillation
  - LMA (Laryngeal Mask Airway)
    - Short-term tube occludes the esophagus
  - Aerosol
    - Nebulized surfactant

Liquid Instillation

- Since the early 1990's surfactants have been researched and instilled via the endotracheal tube (ETT)
- Surfactant studies conducted looked at variety of variables (Pub Med list >1000 articles)
  - Fraction of Inspired Oxygen (FiO_2)
  - Mean Airway Pressure (MAP)
  - Dose (mg)
- No surfactant studies have been conducted with the primary objective/outcome of:
  - "Optimal" way/method to instill surfactant.
  - To find or show differences in Chronic Lung Disease (CLD)"

Let’s Discuss Studies

- Can you believe everything you read?
- What to look for in research
- Retrospective Studies
- Clinical Study
  - Characterized by observable and diagnosable symptoms

InSurE Method

Intubate / Surfactant / Extubate

Verder Study:

- 73 patients enrolled
  - 25 to 35 week gestation (36 treated with surfactant, 37 controls)
  - Age 2 to 72 hours
  - Need for NCPAP ≥ 6 CWP flow rate 10 to 16 lpm
  - Oxygen was by a/a ratio of less than 0.22

InSurE treatment was considered to have failed in infants who were not extubated within one hour or who were reintubated for mechanical ventilation within five days[1]

1. Verder H, Robertson B, Greisen G, et al. Surfactant Therapy and Nasal Continuous Positive Airway Pressure for Newborns with Respiratory Distress Syndrome. N Engl J Med. 1994; 331:1051-1055.

Study Results[1]

Combination of early NCPAP and surfactant therapy reduced the progression of RDS by improving oxygenation and reducing carbon dioxide retention and the need for mechanical ventilation.[1]

1. Verder H, Robertson B, Greisen G, et al. Surfactant Therapy and Nasal Continuous Positive Airway Pressure for Newborns with Respiratory Distress Syndrome. N Engl J Med. 1994; 331:1051-1055.

InSurE Method Questions

- Who is the optimal patient?
- What is the optimal time to instill?
- What are the failure rates of non-invasive vs. mechanical ventilation?
- Are failure rates related to the surfactant or to lung “recruitment”?
- Have there been changes in BPD or outcomes?

InSurE Method Studies

Published data is split on rates of success vs. failures.

"Randomized controlled study comparing INSURE method with nasal CPAP alone in infants of 29 to 35 weeks' gestation, reported a failure rate of 50%." (Reininger, 2005)[1]

"Retrospective study of 115 premature infants, reported a rate of failure of 49%." (Anderson 2006)[2]

"A small randomized trial comparing the INSURE method to MV/SUR in preterm infants <30 weeks' gestation, reported a rate of failure of 15%." (Dani, 2012)[3]

Clinical interpretation of data is at the discretion of the reader.

1. Reininger A, Khalak R, Kendig J, et al. Surfactant Administration by Transient Intubation in Infants 29 to 35 Weeks' Gestation with Respiratory Distress Syndrome Decreases the Likelihood of Later Mechanical Ventilation: A Randomized Controlled Trial. J Perinatology 2005;25:703-708.
2. Anderson T, Holm HS, Kamper J, et al. Surfactant treatment of newborn infants receiving continuous positive airway pressure treatment. Ugeskr Laeger. 2006; 168:3723-3727.
3. Dani C, Corsini L, Poggi C, et al. Risk factors for Intubation-surfactant-extubation (INSURE) failure and multiple INSURE strategy in preterm infants. Early Hum Dev. 2012;88:53-54.

InSurE Method

Indicators that increase the odds of failure:

- Decreasing gestational age
- Low Apgar at 5 minutes
- High FiO_2 requirement
- High pCO_2
- Long duration of mechanical ventilation post instillation

MIST
Minimally Invasive Surfactant Therapy

There are four different MIST methods.[1]

- Pharyngeal Surfactant Administration
- Thin Catheter Administration (TCA) / LISA
- Laryngeal Mask-Guided Surfactant Administration (LMA)
- Aerosolized Administration

None are FDA approved in USA

1. More K, Sakhuja P, Shah P, et al. Minimally Invasive Surfactant Administration in Preterm Infants: A Meta-narrative Review. JAMA Pediatr. 2014;168:901-908.

MIST Studies

MIST Published data – states the need for further investigations.

"We observed moderate MIST failure rates in concordance with the results of earlier studies. Absence of corticosteroids and lower surfactant dose are risk factors for MIST failure that may be modifiable in order to improve MIST success and patient outcomes." (Janssen, 2019)

"There is growing evidence for MIST as an alternative to INSURE procedure in spontaneously breathing preterm infants with RDS. Mist is safe, feasible and effective in pre term infants. However further studies are needed to resolve uncertainties in the MIST method, including infant selection, optimal surfactant dose and administration method and need for sedation." (Shim, 2017)

"As noninvasive forms of ventilation have supplemented an almost universal approach to respiratory support that has included intubation and conventional ventilation, new strategies to deliver surfactant less invasively have been developed. Further studies will aid in determining which patients would benefit most." (Barkhuff, 2019)

Clinical interpretation of data is at the discretion of the reader.

1. Janssen L, VanDerSpoil J, vanKaam A. et al. Minimally invasive surfactant therapy failure: risk factors and outcome. Arch Di Child Fetal Neo ED. 2019;0:F1-F7.
2. Shim G. Update of minimally invasive surfactant therapy. Korean J Pediatr. 2017; 60(9):273-281.
3. Barkhuff W, Stoll RF. Novel Surfactant Administration Techniques: Will they Change Outcome? Neonatology. 2019;115(4):411-422.

More “Studies” Discussion

- Carefully read the last sentence of the discussioin paragraph on the previous slide.

LISA
Less Invasive Surfactant Administration

Also referred to as Thin Catheter Administration (TCA)

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LISA/TCA

Methodology

- Sedation and or analgesia
  - Atropine to reduce secretions
- Catheter
  - Small diameter tube (4 or 5Fr suction or gastric)
- Insertion into the cords (hopefully with non-invasive in place)
  - Nasal (need Magill forceps)
  - Mouth (using laryngoscope)
- Surfactant is instilled slowly over 1 to 3 minutes
  - If baby chokes, de-saturates, becomes bradycardic or stops breathing - stop and provide necessary support
- Remove the catheter after the surfactant is instilled
- Attempt to keep the infant on non-invasive support during instillation

LISA Studies

"A new method of surfactant application was associated with a lower prevalence of mechanical ventilation and better pulmonary outcome. A prospective controlled trial is required to determine whether this approach is superior to standard care." (Kribs, 2010)

"The administration of Beractant using a less invasive surfactant administration technique with specifically designed cannula for administration is feasible." (Ramos-Navarro, 2016)

"Less invasive surfactant therapy improves pulmonary outcomes in preterm neonates with RDS and should ideally be administered in combination with NCPAP. Further studies are needed for timing and dose of surfactant after LISA or similar methods." (Gortner, 2018)

Clinical interpretation of data is at the discretion of the reader.

1. Kribs A, Hartel C, Kattner E, et al. Surfactant without intubation in preterm infants with respiratory distress: first multi-center data. Klin Padiatr. 2010;222(1):13-7.
2. Ramos-Navarro C, Sánchez-Luna M, Zeballos-Sarrato S, et al. Less invasive beractant administration in preterm infants: a pilot study. Clinics (Sao Paulo). 2016;71(3):128-134.
3. Gortner L, Schuller S, Herting E. Review demonstrates that less invasive surfactant administration in preterm neonates leads to fewer complications. Acta Paedia 2018;107:736-743.

LISA

- Regardless of published article's success or failure rates, these were constant:
  - No significant impact on BPD
  - No differences in mortality
  - No severe adverse events
  - Reduced the need for MV

- Were failures related to?
  - Sedation
    - Apnea or RDS severity
  - Surfactant remaining in the catheter
    - Slow trickle can lead to surfactant maldistribution

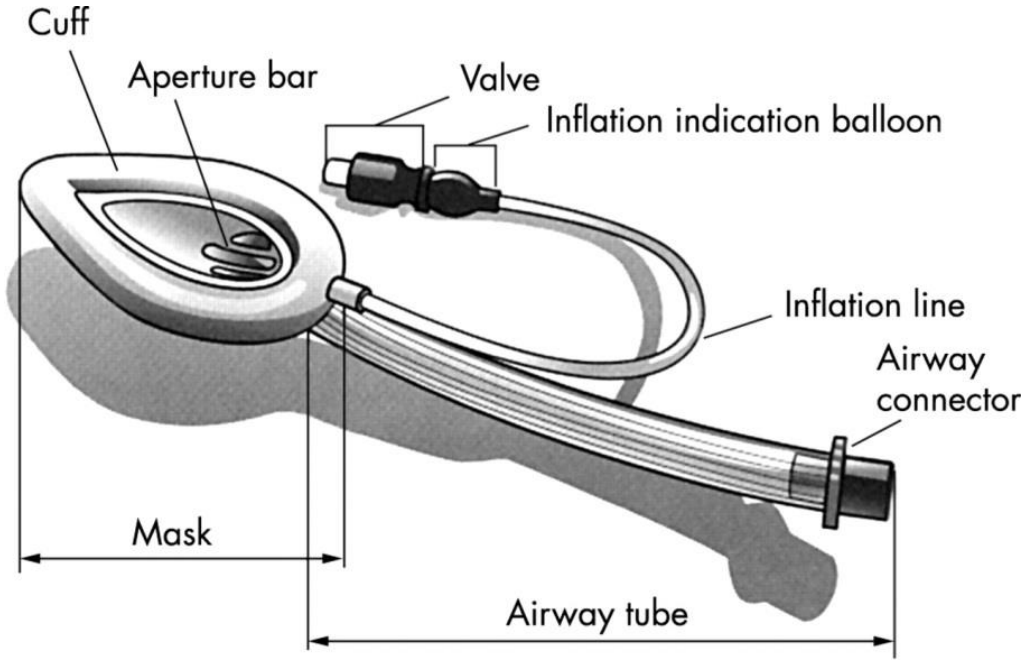
OPTIMIST TRIAL

- Unable to show a decrease in BPD
- However, there are positives to be gleaned from the data

Other LISA/TCA considerations

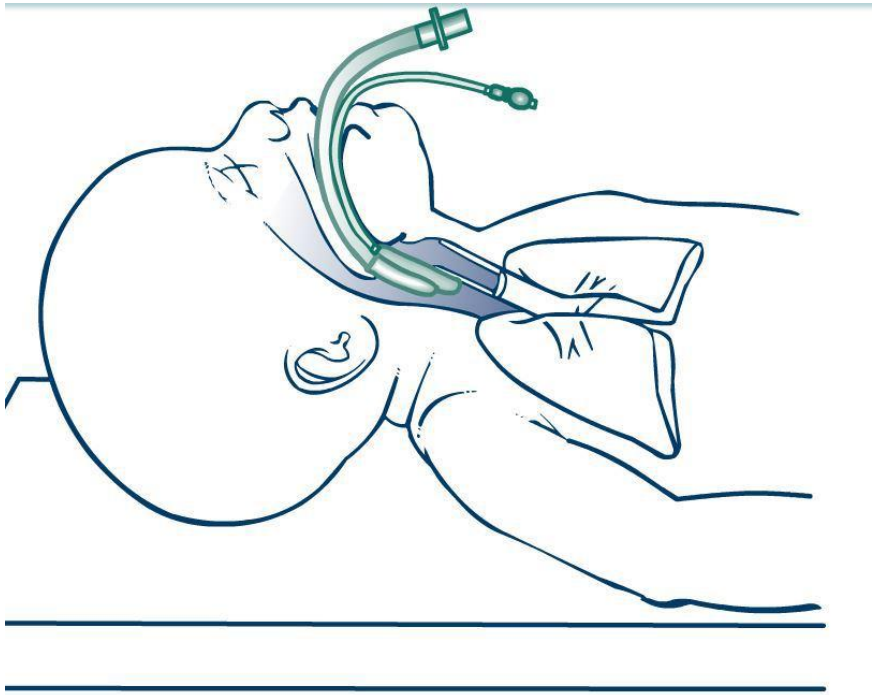
- Not recommended for “severe” RDS
- Not recommended for “older” gestation infants

LMA
Laryngeal Mask Airway



LMA

- Provides alternative to bag mask ventilation
- Short-term airway provided versus intubation
- Allows instillation of surfactant
- Allows for suctioning



LMA Studies

"This pilot study demonstrates that surfactant can be delivered by LMA, which leads to a significant decrease in supplemental oxygen requirement. Larger controlled trials in low-resource settings may show this technique to be valuable in clinical situations where direct laryngoscopy and intubation are difficult or where resources for mechanical ventilation are limited." (Attridge, 2013)

"Surfactant therapy through an LMA decreases the proportion of newborns with moderate RDS who require mechanical ventilation, when compared with a standard endotracheal intubation procedure with sedation. The efficacy of surfactant in decreasing RDS severity appears similar with both methods. Morphine premedication likely contributed to early post-surfactant failures." (Pinheiro, 2016)

"In premature neonates with moderate respiratory distress syndrome, surfactant administered through an LMA decreased the rate of intubation and mechanical ventilation. This intervention may have significant impact on clinical care in both high and low resource settings." (Roberts, 2018)

Clinical interpretation of data is at the discretion of the reader.

1. Attridge JT, Stewart C, Stukenborg GJ, et al. Administration of rescue surfactant by laryngeal mask airway: lessons from a pilot trial. Am J Perinatol. 2013;30(3):201-206.
2. Pinheiro J, Santana-Rivas Q, Pezzano C. Randomized trial of laryngeal mask airway versus endotracheal intubation for surfactant delivery. J Perinatol. 2016;36:196-201.
3. Roberts K, Brown R, Lampland AL, et al. Laryngeal Mask Airway for Surfactant Administration in Neonates: A Randomized, Controlled Trial J Pediatr. 2018;193:40-61

LMA Challenges

- Limited by size thus limiting the treatable population
  - Unable to treat <28 weeks and/or 1.2kg
- No LMA vs. TCA studies have been conducted
- Instillation issues same as liquid and InSurE
  - Brady, reflux, desaturation etc.
- Does LMA provide better deposition and distribution?
  - Providing PPV and PEEP versus just spontaneous RR of LISA
- Current devices **must** disconnect support to give surfactant

Aerosolized Surfactant

- The “Holy Grail” for Surfactant Replacement Therapy?
- Would it be least invasive vs. those less invasive?
- Is there **“NO”** intubation?
- Avoids risks associated with:
  - Positive Pressure Ventilation (PPV)
  - Peak Inspiratory Pressure (PIP)
  - Positive End Expiratory Pressure (PEEP)
- Is there better surfactant distribution?
- What is the treatment timing?

Aerosol

- First aerosolized surfactant reported 1967[1]
- Bert Bunnell submits doctoral thesis related to treatment of Respiratory Distress Syndrome with aerosolized synthetic surfactant in the 1970's.
- From the 1970's to date:
  - Numerous studies have explored the potential for aerosolized surfactant
  - Numerous nebulizers have been tested
  - Numerous companies and academics have tried to aerosolize the natural surfactants or create synthetic/artificial surfactants for aerosolization

1. Chu J, Clements JA, Cotton EK, et al. Neonatal pulmonary ischemia. I. Clinical and physiologic studies. Pediatrics. 1967;40(4): Supp: 709-782.

Challenges in the Development of Aerosol

- Devices
  - Ultrasonic
  - Jet
  - Mesh screen
- Natural and synthetic surfactants
  - Ability to consistently provide mist
- Deposition and distribution
  - Placement
  - Supplemental support impact
  - Surfactant dose volume

Aerosol Questions

- Can “all” natural surfactants be nebulized effectively?
- What duration of treatment time will be needed?
- Is there a waste of surfactant?
- What is the effect on the supporting respiratory equipment?
  - Surfactant clogging up sensors and transducers
- Are the surfactant properties altered?
- Will surfactant reach the distal airways for adsorption?

Aerosol Studies

"No beneficial effects of aerosolized surfactant were demonstrated in our trial, contrary to data from animal experiments. This finding probably reflects differences in administration techniques. Our findings do not justify large clinical trials with the same protocol. Further work is needed to optimize delivery of aerosolized surfactant to the neonatal lung in clinical practice." (Berggren, 2000)

"Seventeen infants were enrolled. Aerosurf was well tolerated, with transient desaturations observed during dosing without bradycardia or hypotension." (Finer, 2010)

"Early postnatal nebulized surfactant may reduce the need for intubation in the first 3 days of life compared with nCPAP alone in infants born at 29^{0}-31^{6} weeks' GA with mild respiratory distress syndrome. Confirmation requires further adequately powered studies." (Minocchieri, 2019)

Clinical interpretation of data is at the discretion of the reader.

1. Berggren E, Liljedahl M, Winbladh B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. Acta Paediatr. 2000;89(4):378-499.
2. Finer NN, Merritt TA, Bernstein G, et al. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. J Aerosol Med Pulm Drug Deliv. 2010;23(5):303-9.
3. Minocchieri S, Berry CA, Pillow JJ, et al. Nebulized surfactant to reduce severity of respiratory distress: a blinded, parallel, randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2019;104:F313–F319.

Summary

- Clinical changes in practice for surfactant instillation have not improved CLD.
- RDS pathophysiology remains surfactant deficiency.
- Continuous positive airway pressure mimics some surfactant properties.
- Has the delay with “watch and wait” made surfactant instillation more difficult?
  - (Is there an increase in atelectasis that could make surfactant instillation into closed alveoli more difficult?)
- Surfactant instillation **via ETT** is the **ONLY FDA APPROVED** method of delivery.

AS WITH ALL PATIENT CARE

- Adapt your care to meet your patient's needs


THANK YOU