

Surfactant (SA) Therapy for Neonatal Pulmonary Diseases

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Disclosure

- Nothing to disclose.

Objectives

1. Summarize surfactant replacement therapy in neonates
2. Review neonatal pulmonary disorders that may benefit from surfactant therapy
3. Understand the role of surfactant in neonatal respiratory physiology

Abbreviations

- SA = surfactant
- PT = preterm
- RDS = respiratory distress syndrome
- MSAF = meconium-stained amniotic fluid
- MAS = meconium aspiration syndrome
- PH = pulmonary hemorrhage
- PPHN = persistent pulmonary hypertension of the newborn
- BPD = bronchopulmonary dysplasia
- PIE = pulmonary interstitial emphysema
- CPAP = continuous positive airway pressure
- INSURE = intubation, surfactant administration, and extubation
- LISA = less invasive surfactant administration

Overview:

Surfactant in Neonatal Pulmonary Disorders

- **Primary SA deficiency**
 - Respiratory failure secondary to **SA deficiency (RDS)** - a major cause of morbidity and mortality in PT infants.
 - SA therapy substantially reduces mortality and respiratory morbidity for this population.
- **Secondary SA deficiency** - also contributes to acute respiratory morbidity in late PT and FT neonates with:
 - **MAS**
 - **Pneumonia/sepsis**
 - **Pulmonary hemorrhage**
 - SA replacement **may be** beneficial for these infants.

RDS: Respiratory Distress Syndrome

- aka Hyaline Membrane Disease
- Caused primarily by deficiency of pulmonary SA in an **immature lung** (ie, developmentally regulated)
- A major cause of morbidity and mortality in PT infants
- The fetal lung is filled with fluid and provides **no** respiratory function until birth
- In preparation for air breathing, **SA is expressed in the lung starting around the 20th week** of gestation.
- **SA reduces the alveolar surface tension** → facilitating alveolar expansion and reducing the likelihood of alveolar collapse/atelectasis.

RDS

- Surfactant (SA) replacement – established as an effective and safe therapy for immaturity-related SA deficiency (RDS) by the early 1990s.
- Systematic reviews of Randomized Controlled Trials (RCT):
 - prophylactic SA administration in PT infants or as rescue therapy for PT with established RDS:
 - reduces mortality
 - decreases the incidence of air leak (pneumothoraces and PIE)
 - lowers the risk of chronic lung disease or death at 28d of age, and improved survival without BPD.

RDS

- SA trials have included:
 - 23 to 34 wks gestation
 - Birth Weight = 500 to 2000g
- SA therapy decreased mortality rates most effectively in:
 - < 30 wks gestation
 - Birth Weight < 1250g
- Recent RCTs:
 - Benefits of prophylactic SA are no longer evident in groups of infants when **continuous positive airway pressure (CPAP)** is used routinely. (Non-invasive ventilation (**NIV**))

RDS and Surfactant Rx

- **Prophylactic, or preventive SA strategy**
 - intubation and SA administration to infants at high risk of developing RDS for the primary purpose of **preventing worsening RDS** rather than treatment of established RDS
 - SA administration in the delivery room before initial resuscitation efforts or the onset of respiratory distress
 - mostly, after initial resuscitation but **within 10-30 min after birth**.
- **Rescue or treatment SA strategy**
 - SA is given only to PT **infants with established RDS**.
 - most often administered **within the first 12 hours after birth**, when specified threshold criteria of severity of RDS are met.
 - Early rescue → within 1-2 h of birth,
 - Late rescue → 2 or more hours after birth.

Surfactant use: **Caution!**

- Delivery of SA can result in rapid improvement in:
 - Lung volume
 - Functional residual capacity
 - Compliance
- Expeditious changes in mechanical ventilator settings may be necessary to minimize the risks of lung injury and air leak.
 - Volume ventilators vs Pressure ventilators

Commercial SA products

- **Animal-derived**
 - Beractant (Survanta) minced bovine lung extract
 - Calfactant (Infasurf) bovine calf lung lavage
 - Poractant (**Curosurf**) minced porcine lung extract
 - **Synthetic**
 - Colfosceril (Exosurf)
 - **Synthetic, protein analog**
 - Lucinactant (Surfaxine)
- **Phospholipid (mg)**
 - 25
 - 35
 - 80
 - 13.5
 - 30

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- **Suggested Dose (ml/kg)**
 - 4
 - 3
 - 2.5; 1.25 (second dose, prn)
 - 5
 - 5.8

Surfactant use

- SA administration strategies have been based on manufacturer guidelines for individual SA.
- The dose of SA, frequency of administration, and treatment procedures have been modeled after research protocols.
- Given the long half-life for SA in PT infants with RDS, redosing should not be needed more often than every 12 h, unless SA is being inactivated by an infectious process, meconium, or blood.
- Dosing intervals shorter than 12h recommended by some manufacturers are not based on human pharmacokinetic data.

Let's review!

**Surface Tension, Lung Surfactant
and Lung Function**

Surface Tension & Lung Function

- At end expiration, surface tension is ~ 0 mN/m, so there is no collapsing force and alveoli remain open.
 - **La Place Law: $P = 2T/r$**
- As each alveolus expands its surface tension keeps rising, generating a force that brakes further expansion, and providing the mechanism for equal aeration of all ~ 3 M to 300 M alveoli.
 - **Delivery of SA can result in improvement in:**
 - Lung volume
 - Functional residual capacity
 - Compliance

Surfactant

- **Def:**

It is the surface active agent

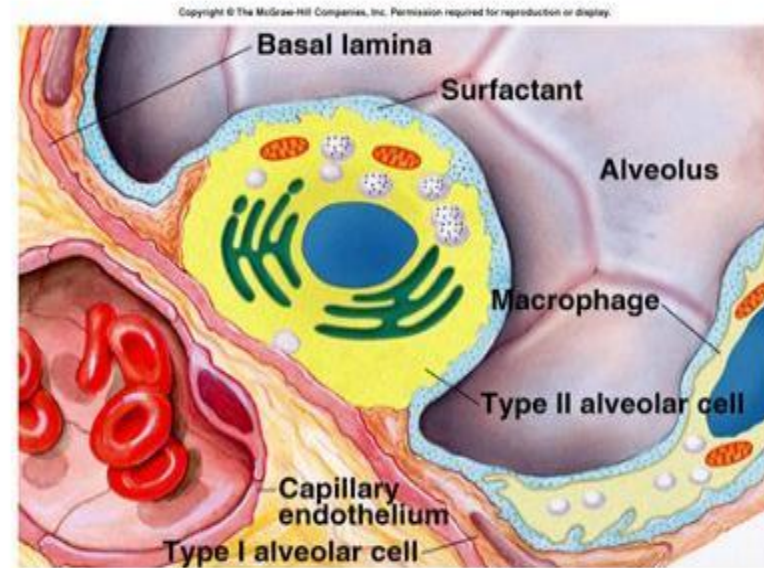
- **Composition:** Phospholipid (dipalmitoyl lecithin), protein and Carbohydrates

- **Secretion:** produced by alveolar type II cells.

- **Action:** Lowers surface tension.

- **Functions of surfactant:**

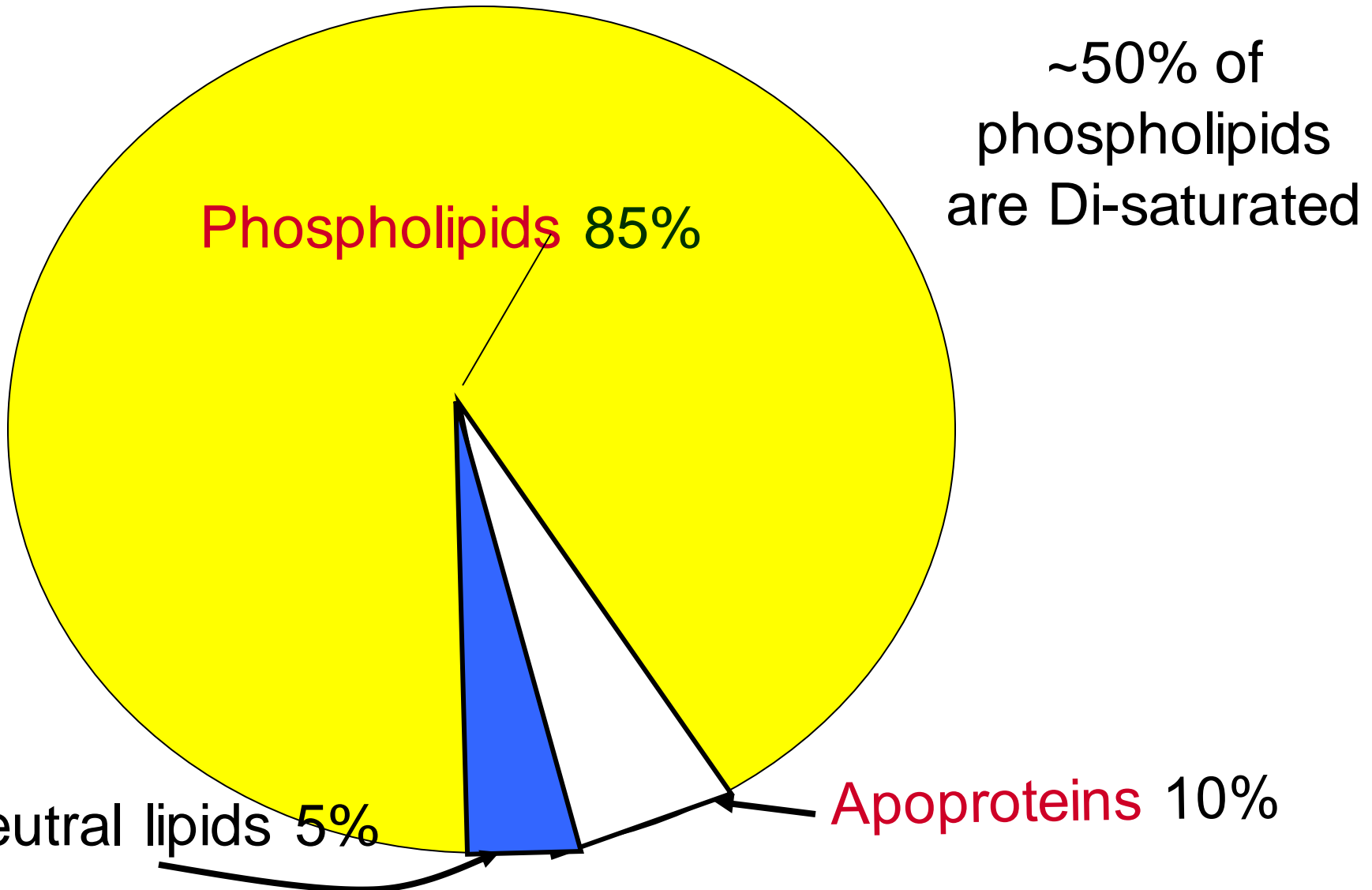
- 1) Facilitates lung expansion
- 2) Prevent lung collapse As alveoli radius decreases, surfactant's ability to lower surface tension increases.
- 3) Prevent pulmonary oedema



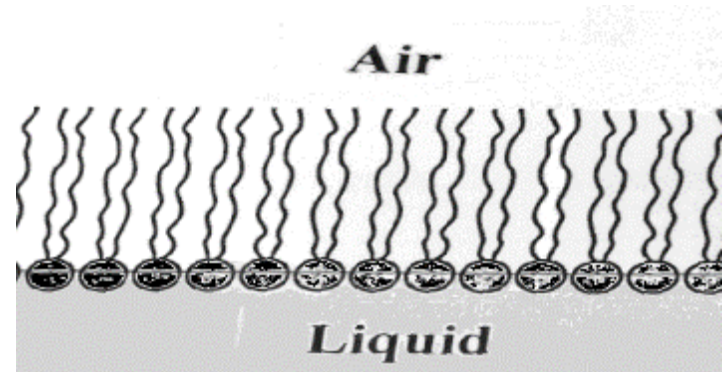
Surfactant Deficiency:

RDS of the newborn. The lung is rigid and oedematous and the alveoli collapse

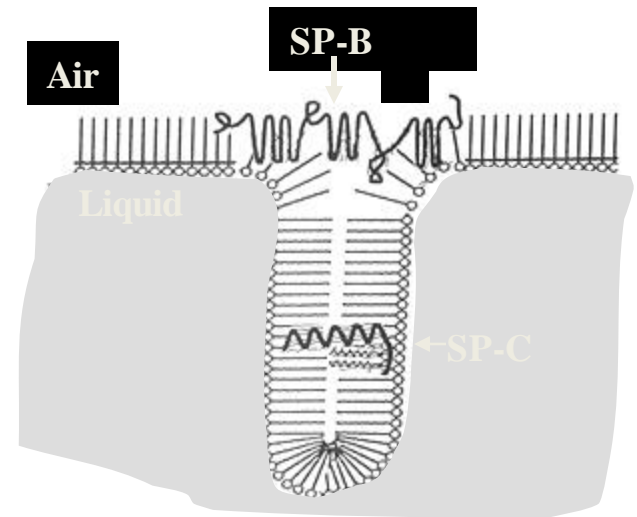
Natural Lung SA composition



SA phospholipids
form a surface film



Hydrophobic proteins
SP-B & SP-C insert lipids onto
the surface to move them in
and out of the film during
breathing



	Infasurf (calfactant)	Curosurf (poractant alfa)	Survanta (beractant)
Source	calf lung surfactant	minced <u>pig</u> lung tissue	minced <u>cow</u> lung tissue
Lipids	surfactant only	surfactant + lung tissue	surfactant+ lung tissue+ synthetic
Proteins			
SP-B	0.7%	0.38%	<0.1%
SP-C	1.0%	0.88%	1.0%

Surfactant Therapy

SUMMARY

Surfactant replacement therapy for PT and term neonates with respiratory distress. (Ref: *Pediatrics* 2014;133;156)

- Respiratory failure secondary to SA deficiency is a major cause of morbidity and mortality in PT infants. SA therapy substantially reduces mortality and respiratory morbidity for this group of patients.

– Standard of care in RDS!

- Secondary SA deficiency also contributes to acute respiratory morbidity in late-PT and term neonates with MAS, pneumonia/sepsis, and possibly pulmonary hemorrhage; SA replacement *may be* beneficial for these infants.

– Standard of care? (MAS?, Pneumonia?, Pulm hge?)

Surfactant Therapy: Summary of the Science

Pediatrics 2014;133;156

1. SA replacement, given as prophylaxis or rescue treatment, reduces the incidence of RDS, air leaks, and mortality in preterm infants with RDS (level of evidence (LOE 1)).
2. Both animal-derived and newer synthetic SA with SP-B–like activity decrease acute respiratory morbidity and mortality in PT infants with RDS (LOE 1).
3. Early rescue SA treatment (<2 h of age) in infants with RDS decreases the risk of mortality, air leak, and CLD in PT infants (LOE 1).
4. Early initiation of CPAP with subsequent selective SA administration in extremely PT infants results in lower rates of BPD/death when compared with treatment with prophylactic SA therapy (LOE 1).

Surfactant Therapy: Summary of the Science

5. SA replacement has not been shown to affect the incidence of neurologic, developmental, behavioral, medical, or educational outcomes in preterm infants (LOE 2).
6. Antenatal steroids and postnatal SA replacement independently and additively reduce mortality, the severity of RDS, and air leaks in PT infants (LOE 2).

SA Replacement Rx: Clinical Implications

- PT infants born at <30 wks gestation who need mechanical ventilation because of severe RDS should be given SA after initial stabilization. (Strong Recommendation).
- Using CPAP immediately after birth with subsequent selective SA administration should be considered as an alternative to routine intubation with prophylactic or early SA administration in preterm infants. (Strong Recommendation).

SA Replacement Rx: Clinical Implications

- Rescue SA may be considered for infants with hypoxic respiratory failure attributable to secondary SA deficiency (eg, pulmonary hemorrhage, MAS, or sepsis/pneumonia) (Recommendation).
- Preterm and term neonates who receive SA should be managed by nursery and transport personnel with the technical and clinical expertise to administer SA safely and deal with multisystem illness. Therefore, pediatric providers who are without expertise, or who are inexperienced or uncomfortable with SA administration or managing an infant who has received SA should wait for the transport team to arrive.

INSURE (INtubation-SURfactant-EXTubation)

In preterm infants with RDS, INSURE has been found to reduce the:

- need for MV
- duration of respiratory support
- need for SA

!!! This method **may fail** in some patients with:

- Birth Weight < 750 g
- $pO_2/FiO_2 < 218$
- $a/ApO_2 < 0.44$ (arterial/Alveolar oxygen tension ratio)

as the first ABG were independent risk factor for INSURE failure in <30 wks AOG infants.

INSURE (INtubation-SURfactant-Exttubation)

INSURE treatment can be repeated (respiratory outcome similar in infants treated with single or multiple INSURE procedures).

It is possible that the multiple INSURE strategy might decrease the failure rate of INSURE and increase its effectiveness in preventing the need for mechanical ventilation (MV).

CPAP for RDS

Extremely PT infant during nCPAP care. (Note loose fitting of nasal prongs, comfortable nesting and positioning of infant).



Key points for CPAP care

1. Infants on CPAP are completely dependent on open nasal passages.
2. Find the optimal body position for the infant (NIDCAP).
3. Use PT pacifier to minimize loss of pressure from open mouth.
4. Try to avoid suctioning the nose and use saline drops instead, then suction the oropharynx.
5. Use adequate humidification of gases.
6. Avoid using excessive force when fixating the nasal prongs.
7. The nosepiece should not be pulled tightly against the nose, rather positioned from under the nose.
8. Use the largest size prong that will sit without support in the nose.
9. Inspect the fixation when you see that the nosepiece is pressing too tightly against the nose or the CPAP pressure is difficult to hold.
10. Change to a larger prong as the baby grows.

AAP Committee on Fetus and Newborn: Resp Support in PT Infants at Birth

(Ref: *Pediatrics* 2014, 133(1):171-174)

- Current practice guidelines recommend administration of SA at or soon after birth in PT infants with RDS.
- However, recent multicenter randomized controlled trials indicate that early use of CPAP with subsequent selective SA administration in extremely PT infants results in lower rates of BPD/death when compared with treatment with prophylactic or early SA therapy.
- **CPAP started at or soon after birth** with subsequent selective SA administration may be **considered as an alternative to routine intubation with prophylactic or early SA administration in PT infants.**

AAP: Conclusions

1. Based on a meta-analysis of prophylactic SA versus CPAP as well as on other trials of more selective early use of SA versus CPAP not included in the meta-analysis, the early use of CPAP with subsequent selective SA administration in extremely PT infants results in lower rates of BPD/death when compared with treatment with prophylactic or early SA therapy (Level of Evidence: 1).
2. PT infants treated with early CPAP alone are not at increased risk of adverse outcomes if treatment with SA is delayed or not given (Level of Evidence: 1).

AAP: Conclusions

3. Early initiation of CPAP may lead to a reduction in duration of mechanical ventilation and postnatal corticosteroid therapy. (Level of Evidence: 1).

4. Infants with RDS may vary markedly in the severity of the respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care.

Care for these infants is provided in a variety of care settings, and thus the capabilities of the health care team need to be considered.

AAP: Recommendation

1. Using CPAP immediately after birth with subsequent selective SA administration may be considered as an alternative to routine intubation with prophylactic or early SA administration in PT infants.

(Level of Evidence: 1, Strong Recommendation).

2. If it is likely that respiratory support with a ventilator will be needed, early administration of SA followed by rapid extubation is preferable to prolonged ventilation.

(Level of Evidence: 1, Strong Recommendation)

Other Surfactant Deficiency States

Meconium Aspiration Syndrome (MAS)

- MAS is defined as respiratory distress in newborn infants born through meconium-stained amniotic fluid (MSAF) whose symptoms cannot be otherwise explained.
- MAS can present with varying degrees of severity from mild respiratory distress to life-threatening respiratory failure.
- The best approach for managing MAS is prevention.

MAS – Intrapartum Mx

- **Intrapartum care to reduce the incidence of MAS includes:**
 - Prevention of fetal hypoxia
 - Prevention of postmature (>41 or 42 wks gestation) delivery
- **Prevention of fetal hypoxia**
 - Continuous or periodic intrapartum fetal heart rate (FHR) monitoring has become a standard of care in the US, particularly in pregnancies thought to be at higher risk for **intrapartum fetal hypoxemia** (eg, postterm pregnancy, intrauterine growth restriction, preeclampsia).
 - the value of intrapartum fetal monitoring to predict fetal hypoxemia and subsequent intervention in cases with abnormal traces in preventing MAS has not been proven.

MAS – Intrapartum Mx

- **Prevention of postmature delivery**
 - Because the risk of MAS is greatest in infants with a gestational age > 41 wks, preventing delivery after 41 wks gestation reduces the incidence of MAS.
 - For women greater than 41 wks gestation, induction of labor rather than expectant management is recommended.
- **Amnioinfusion**
 - the instillation of isotonic fluid into the amniotic cavity.
 - proposed benefits of amnioinfusion include: dilution of thick clumps of meconium by the instilled fluid, and possible prevention or relief of cord compression.
 - not beneficial in reducing meconium-related neonatal morbidity. As a result, amnioinfusion is **not** recommended as a routine approach for mothers with MSAF.

MSAF – L&D

- No benefit of intrapartum suctioning in infants with MSAF
- After delivery, the guidelines from the International Liaison Committee on Resuscitation (ILCOR), American Academy of Pediatrics (AAP), and the American Heart Association (AHA) **do not recommend suctioning** in the **vigorous** infant with MSAF, as it does not improve outcome and may cause complications
- Infants with MSAF who exhibit signs of respiratory distress in the delivery room are observed in the NICU or Special Care Nursery for 4-6 hours to ensure they transition successfully. Asymptomatic infants with Apgar scores ≥ 9 can be admitted to the normal nursery without additional monitoring or intervention.

MAS - Management

- **The general approach to care includes:**
 - Maintenance of adequate oxygenation and ventilation
 - Maintenance of adequate blood pressure and perfusion
 - Correction of any metabolic abnormality including hypoglycemia and acidosis, which increase O₂ consumption
 - Empirical antibiotic therapy
 - Care in a neutral thermal environment (unless there are signs of hypoxemic ischemic encephalopathy, which is treated with hypothermia)
 - Minimal handling of the infant to avoid agitation, which exacerbates persistent pulmonary hypertension of the newborn (PPHN), if present

MAS - Respiratory Mx

- Focused on maintaining optimal oxygenation and ventilation, especially as hypoxemia, acidosis, and hypercapnia, which may increase pulmonary vascular resistance and contribute to the development of PPHN
- Hyperventilation, respiratory alkalosis, and air-trapping **should be avoided.**
- Supplemental O₂ therapy is usually adequate in patients with mild or moderate disease.
- In patients with severe disease, interventions may include MV, HFOV, SA therapy, and/or inhaled NO therapy.
- In patients with respiratory failure who have failed to respond to other interventions, extracorporeal membrane oxygenation (ECMO) may be a life-saving intervention.

MAS - O₂ Rx

- Supplemental O₂ therapy should be initiated to keep the infant well saturated (SaO₂ > 99 %) while diagnostic tests are performed.
- When the diagnosis is established, arterial PO₂ should be maintained in the range of 55 to 90 mmHg (SaO₂ > 90 %) to provide adequate tissue oxygenation and avoid lung injury that may result from continued administration of high concentrations of O₂.
- Hypoxemia should be avoided because it contributes to pulmonary vasoconstriction and possibly PPHN.
- Umbilical arterial and venous (multiple lumen) catheters are used to monitor arterial blood gases and blood pressure, and infuse fluids and medications.

MAS - Assisted Mechanical Ventilation (MV)

- Assisted MV is used when gas exchange is not adequate with spontaneous breathing. When FiO_2 exceeds 0.4 to 0.5, CPAP may improve oxygenation. CPAP should be used cautiously in infants with hyperinflation as it may exacerbate air trapping.
- Approximately 30 % of patients with MAS require MV due to respiratory failure.
- Goal for assisted MV is to achieve **optimal gas exchange** with minimal respiratory trauma. In MAS, target $PaCO_2$ levels between 50 to 55 mmHg and arterial PO_2 between 55 to 90 mmHg ($SaO_2 >90\%$).
- Consider using **HFOV** in infants who fail to respond to CMV, and in those who fail MV and pharmacologic treatment, ECMO therapy.

MAS - Surfactant

- SA **may** reduce the severity of respiratory disease and reduce the need for ECMO in mechanically ventilated infants.
- Findings in a meta-analysis of four trials: 326 infants (2014):
 - **no difference** in mortality rate between infants who received SA vs placebo
 - SA **reduced** the need for ECMO therapy (two studies, 208 infants)
 - SA, vs placebo, **did not reduce** the risk of pneumothorax (three studies), pulmonary interstitial emphysema (PIE) (one study), chronic lung disease (CLD) (one study), air leaks (one study), duration of mechanical ventilation (MV) (three studies) or oxygen therapy (two studies), or intraventricular hemorrhage (two studies).

MAS - Surfactant

- SA use with MAS is **not routine**.
- **Recommendations:**
 - Administer SA (150 mg/kg [**6mL/kg**]) to patients with severe MAS:
 - mechanically ventilated
 - and require high FiO_2 (>0.5)
 - and high mean airway pressure (>10 to $12 \text{ cmH}_2\text{O}$)
 - SA may also be helpful in infants with radiographic evidence of SA dysfunction (eg, low lung volumes and homogeneous pulmonary parenchymal disease that is similar in appearance to RDS).

MAS – Surfactant lung lavage

- Insufficient data to determine its benefit.
- Meta-analysis, (3 trials), reported no differences in the two separate outcomes of mortality and the use of ECMO for patients treated with SA lavage and controls, but the lavage group had a better outcome with a composite outcome of death or the use of ECMO.
 - Limitations: small number of patients, and the differences in study design (eg, severity of disease, volume of lavage, and use of subsequent bolus of SA)
 - SA tracheobronchial lavage **not** routinely recommended.
 - May be warranted in patients with severe disease, in centers without **ECMO capabilities** and who are experienced in performing this.
 - SA lavage in mechanically ventilated infants is technically demanding and is associated with serious complications. Larger RCT is required before SA lavage can be routinely recommended for infants with severe MAS.

SA in Pneumonia/Sepsis

- **SA inactivation** may be associated with pneumonia.
- RCT of SA rescue therapy, the subgroup of infants with sepsis showed **improved oxygenation and a reduced need for ECMO** compared with a similar group of control infants.
- Newborn infants with pneumonia or sepsis receiving rescue SA also demonstrated improved gas exchange compared with infants without SA treatment.
- The number of neonates who received SA for sepsis and pneumonia in these clinical reports is small, and **no recommendation can be made.**

SA in Pulmonary Hemorrhage

- **Pulmonary hemorrhage:**
 - SA treatment rationale: **blood inhibits SA function.**
 - Only a few retrospective and observational reports have documented the benefits of such therapy, and the **magnitude of benefit remains to be established.**

SA in CDH (Congenital Diaphragmatic Hernia)

- **CDH:**
 - Congenital diaphragmatic hernia may be associated with **SA insufficiency**.
 - Although measurements of disaturated phosphatidylcholine from lungs of infants with CDH show synthetic rates similar to those from infants without diaphragmatic hernia, pool sizes and kinetics are altered.
 - However, SA treatment of a large series of infants with CDH **did not improve outcomes**. In fact, the need for ECMO, the incidence of chronic lung disease, and mortality rate were increased with SA administration.

Summary

Surfactant replacement therapy for PT and term neonates with respiratory distress. (Ref: *Pediatrics* 2014;133;156)

- Respiratory failure secondary to SA deficiency is a major cause of morbidity and mortality in PT infants. SA therapy substantially reduces mortality and respiratory morbidity for this population.

– Standard of care!

- Secondary SA deficiency contributes to acute respiratory morbidity in late-PT and term neonates with MAS, pneumonia/sepsis, and pulmonary hemorrhage; **SA replacement may be beneficial for these infants.**

– Standard of care? (MAS?, Pneumonia?, Pulm hge?, CDH)

Surfactant replacement therapy for PT and term neonates with respiratory distress. (Ref: *Pediatrics* 2014;133;156)

SA treatment improves oxygenation and reduces the need for ECMO without an increase in morbidity in neonates with MAS (LOE 2).

SA treatment of infants with congenital diaphragmatic hernia does not improve clinical outcomes (LOE 2).

Thank you!

Questions?