Respiratory Distress Syndrome (RDS)

INTRODUCTION: RDS, also known as hyaline membrane disease, is the commonest respiratory disorder in preterm infants. The clinical diagnosis is made in preterm infants with respiratory difficulty that includes tachypnea, retractions, grunting respirations, nasal flaring and need for ↑ FiO_2. In the last three decades, introduction of antenatal steroids and exogenous surfactant has greatly improved outcomes in RDS; however, it remains a principal clinical problem.

EPIDEMIOLOGY: RDS affects 40,000 infants each year in the US and accounts for approximately 20% of neonatal deaths. RDS typically affects infants <35 weeks gestational age (GA) but may affect older infants who have delayed lung maturation. Low GA is the greatest risk factor for RDS, and its incidence varies inversely with birth weight among AGA infants (Table 1). Other factors may also influence the risk of RDS among preterm infants (Table 2).

Table 1. Incidence of RDS by Birth Weight.

Birth Weight (g)	Incidence of RDS
501-750	86%
751-1,000	79%
1,001-1,250	48%
1,251-1,500	27%

Table 2. Other risk factors for RDS.

Increased Risk	Decreased Risk
Prematurity	Chronic intra-uterine stress
Male gender	Prolonged rupture of membranes
Familial predisposition	Maternal hypertension or toxemia
Cesarean section without labor	IUGR/SGA
Perinatal asphyxia	Antenatal glucocorticoids
Caucasian race	Maternal use of narcotics/cocaine
Infant of diabetic mother	Tocolytic agents
Chorioamnionitis	Hemolytic disease of the newborn
Non-Immune hydrops fetalis	

PATHOPHYSIOLOGY: The primary cause of RDS is inadequate pulmonary surfactant. The structurally immature and surfactant-deficient lung has ↓ compliance and a tendency to atelectasis; other factors in preterm infants that ↑ the risk of atelectasis are decreased alveolar radius and weak chest wall. With atelectasis, well perfused but poorly ventilated areas of lung lead to V/Q mismatch (with intra-pulmonary shunting) and alveolar hypoventilation with resultant hypoxemia and hypercarbia. Severe hypoxemia and systemic hypoperfusion result in decreased O_2 delivery, anaerobic metabolism and

subsequent lactic acidosis. Hypoxemia and acidosis may further impair oxygenation by causing pulmonary vasoconstriction, resulting in right-to-left shunting at the levels of the foramen ovale and ductus arteriosus.

Other factors, such as baro/volutrauma and high FIO_2, may initiate release of inflammatory cytokines and chemokines causing more endothelial and epithelial cell injury. The injury results in reduced surfactant synthesis and function as well as increased endothelial permeability leading to pulmonary edema. Leakage of proteins into the alveolar space further exacerbates surfactant deficiency by causing surfactant inactivation. Macroscopically, the lungs appear congested, atelectatic and solid. Microscopically, diffuse alveolar atelectasis and pulmonary edema are seen. An eosinophilic membrane composed of a fibrinous matrix of materials from the blood and cellular debris (the hyaline membrane) lines the visible airspaces that usually constitute dilated terminal bronchioles and alveolar ducts.
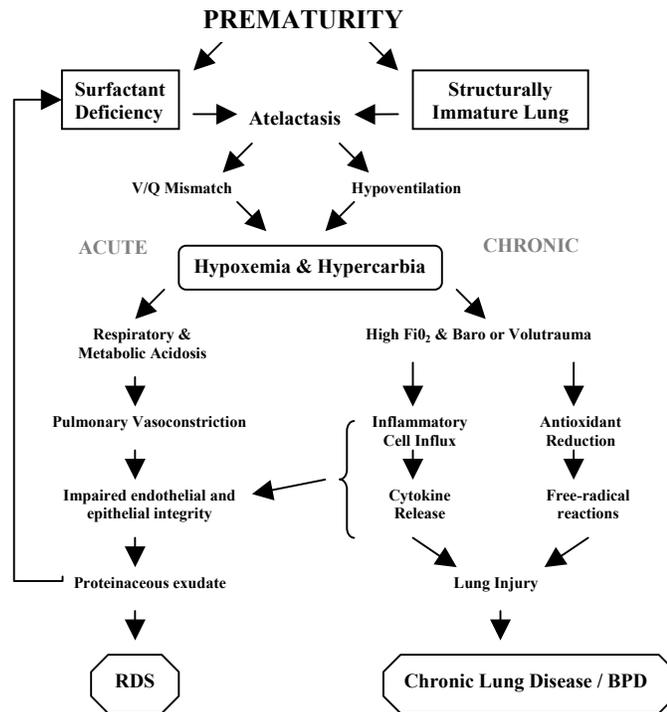
CLINICAL FEATURES: Signs of RDS appear immediately after birth or within 4 h. RDS is characterized by tachypnea (>60 breaths/min), intercostal and subcostal retractions, nasal flaring, grunting, and cyanosis in room air. Tachypnea is due to an attempt to increase minute ventilation to compensate for a decreased tidal volume and increased dead space. Retractions occur as the infant is forced to generate a high intrathoracic pressure to expand the poorly compliant lungs. Grunting results from the partial closure of the glottis during forced expiration in an effort to maintain FRC.   After an initial improvement with resuscitation and stabilization, an uncomplicated course is often characterized by a progressive worsening for 48 to 72 h. Recovery usually coincides with a diuresis after an initial period of oliguria. Other clinical features may include hypotension, acidosis and hyperkalemia. The typical chest radiograph shows low lung volumes and a bilateral, reticular granular pattern (ground glass appearance) with superimposed air bronchograms. In more severe cases, there is complete "white out" of the lung fields. Application of positive airway pressure may minimize or even eliminate these radiographic findings. Acute complications include air leaks and intracranial hemorrhage. Long-term, RDS has been associated with an increased incidence of chronic lung disease, ROP, and neurologic impairment.

MANAGEMENT: The goals of management of an infant with RDS are to:
    •Avoid hypoxemia and acidosis

•Optimize fluid management: avoid fluid overload and resultant body and pulmonary edema while averting hypovolemia and hypotension
•Reduce metabolic demands and maximize nutrition
•Minimize lung injury secondary due to volutrauma and oxygen toxicity

The three most important advances in prevention and treatment of RDS have been: (a) antenatal glucocorticoids, (b) continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP), and (c) surfactant replacement therapy. These have dramatically decreased morbidity and mortality from RDS.

1. <u>Antenatal glucocorticoids</u> accelerate fetal lung maturity by increasing formation and release of surfactant and maturing the lung morphologically. Physiologic stress levels of corticosteroids administered to the mother initiate a receptor-mediated induction of specific developmentally regulated proteins in the fetus. Administration of glucocorticoids at least 24 to 48 h (and no more than 7 d) before preterm delivery decreases both incidence and severity of RDS. They are most effective before 34 weeks. However, antenatal steroids should still be considered when therapy is less than 24 h before anticipated delivery because a reduction in neonatal mortality and RDS can still occur in this time frame. Repeated (>3) courses of corticosteroids have been associated with decreased fetal growth and poorer neurological outcomes. Antenatal steroids also reduce the incidence of intraventricular hemorrhage, an effect that is independent of lessened pulmonary morbidity and that may be secondary to stabilization of cerebral blood flow or maturation of cerebral vasculature. The effects of antenatal steroids and surfactant have been demonstrated to be additive in improving lung function.

2. <u>Exogenous surfactant</u>: It has been shown in multiple randomized controlled trials that the use of exogenous surfactant in preterm infants improves oxygenation, decreases air leaks, reduces mortality due to RDS, and decreases overall mortality.

  A. Timing of surfactant administration: Two approaches have been used for surfactant delivery: prophylactic and rescue treatment. **Prophylactic administration** involves giving surfactant soon after birth, as soon as the infant has been stabilized. The theoretical benefit of this approach is that replacement of surfactant before RDS develops will avoid or ameliorate lung injury. Animal studies have shown that the lung epithelium of very premature subjects can be damaged within minutes of onset of ventilation. The damage can result in protein leak which subsequently interferes with surfactant function. **Rescue administration** involves giving surfactant to infants who have established RDS and require mechanical ventilation and supplemental O_2. The advantage of this approach is that patients are not treated unnecessarily. Because surfactant currently can only be given via an endotracheal tube, this would prevent intubation and mechanical ventilation of infants who would do well without surfactant and avoid unnecessary baro/volutrauma, adverse physiological effects of laryngoscopy, and possible inadvertent hyperventilation. Past studies have shown greater reduction in neonatal mortality with prophylactic administration versus rescue, especially in infants greatest at risk for RDS (*i.e.*, <27 weeks GA). However, with the use of nasal CPAP in VLBW infants and higher rates of antenatal steroid administration, there exists controversy on the optimal timing of surfactant administration, balancing the benefits of early surfactant administration

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with the advantages of avoiding mechanical ventilation and volutrauma. The current approach to the timing of surfactant therapy at UCSF is summarized in Table 3.

Table 3. Guidelines for intubation and timing of surfactant administration in preterm infants.

Gest. Age (Weeks)	Antenatal Steroids*	Ventilatory Treatment	Timing of Surfactant
≤27	No	Intubate all infants	Prophylactic
≤27	Yes	(a) If intubation[†] & mech. vent. needed at birth	Prophylactic, unless in room air by age 20 min
		(b) Early CPAP, if not stable intubate[†] & mech. vent.	Rescue
		(c) Early CPAP, if stable	Do not give surfactant
27-34	Yes or No	Manage as for ≤27 weeks and (+) steroids	
>34		Use clinical assessment	

*Steroid therapy indicates mother received 2 doses at least 24 h before and not more than 7 d before birth.
[†]For indications for intubation, see Table 4.

B. Administration and dose of surfactant: For prophylactic administration, the position of the endotracheal (ET) tube should be verified by two people before surfactant is given. Attach the surfactant syringe to the side port of the ET tube, occlude end of ET tube, and administer surfactant as a single aliquot over ≈ 5 sec. For rescue therapy, obtain chest radiograph to confirm tube position. Administer surfactant through a feeding tube inserted to (but not past) the end of the ET tube. Administer in same manner as with prophylactic treatment. Slower administration may interfere with its efficacy. After administration, the infant should be hand ventilated and may transiently require higher ventilatory support. Several studies have shown that two doses, 12 h apart, may be more effective than single dose therapy. More than 2 doses is rarely required and is rarely effective. **The dose of surfactant is:**

 Infasurf™   **3mL/kg**
 Survanta™   **4 mL/kg**

C. Criteria for rescue treatment: Rescue treatment with surfactant should be given to preterm infants who have:
 •Respiratory distress, necessitating intubation and assisted ventilation,
 •No radiological evidence of another disease process,

and require either
•$FIO_2 > 0.3$ *or* a mean airway pressure ≥ 7 cmH$_2$O

D. Complications: Although surfactant administration is relatively safe, complications include obstruction of the endotracheal tube, transient increases in O$_2$ requirement and ventilatory settings, and pulmonary hemorrhage, an infrequent adverse effect reported in 2-6% of infants given surfactant.

3. <u>Oxygen</u> should be administered to preterm infants in concentrations sufficient to maintain PaO$_2$ between 50-70 mmHg or saturation (by pulse oximetry) between 85-92%. Higher O$_2$ concentrations may exacerbate lung injury and will increase the risk of retinopathy of prematurity.

4. <u>Respiratory Management</u>: Please see the section on Respiratory Support (P. 10) for a more complete discussion of ventilation strategies. The initial decision in respiratory management of an infant with RDS is whether the infant can be adequately managed with nasal CPAP (*i.e.*, no treatment with surfactant) or should receive endotracheal intubation, surfactant therapy and mechanical ventilation. Endotraheal intubation should be performed in infants that require prophylactic surfactant administration or who meet the criteria listed in Table 4.

Table 4. Indications for intubation of preterm infant during resuscitation.

•GA ≤ 27 weeks and no maternal steroids

•For other infants, <u>any</u> of the following:

-Apnea	-Unable to maintain an adequate airway
-Requires $FIO_2 > 0.4$	- ↑ work of breathing (grunting, retractions, flaring)
-pH <7.25	-PaCO$_2$ >60 mmHg

The goals of ventilatory management in the intubated infant are to maintain adequate oxygenation and ventilation while minimizing ventilator induced lung injury. To achieve these aims, utilize a strategy of permissive hypercarbia, maintaining PaCO$_2$ between 45-55 mmHg, theoretically reducing volutrauma and preventing deleterious effects of hypocarbia. To reduce further the risk of volutrauma, adjust ventilatory pressures to maintain tidal volume between 4-5 mL/kg. Administration of surfactant improves lung mechanics (↑ lung compliance) and increases oxygenation by reducing atelectasis and increasing FRC. It is extremely important to recognize the time frame of these changes. **After surfactant administration, there may be very rapid improvements in pulmonary function that necessitate rapid weaning of ventilator settings.** Close attention must be paid to tidal volume, blood gas tensions, transcutaneous CO$_2$ and pulse oximetry values in order to avoid inadvertent hyperventilation, hyperoxia and over-distension of the lung, all of which can result in lung injury. Although it may be necessary to wean FIO_2, inspiratory pressure and ventilator rate, one should decrease PEEP with extreme caution. Infants in the **early phases of RDS will rarely maintain**

adequate lung inflation if PEEP is <5 cmH$_2$O, even after administration of surfactant.

Recently, much effort has been directed towards other, less invasive modalities of respiratory support to prevent lung injury, specifically nasal CPAP. CPAP, as treatment for RDS, was first described in 1971 by George Gregory at UCSF. Modifications in the nasal CPAP delivery system have generated renewed interest in nasal CPAP for the ventilatory management of RDS. Randomized controlled trials have shown a decreased need for mechanical ventilation in VLBW infants treated with nasal CPAP, although the impact on mortality and chronic lung disease have not been defined. Furthermore, recent reports indicate that **approximately 70% of infants with birth weight <1,000 g will not be adequately managed with nasal CPAP** and will require intubation and mechanical ventilation. Nevertheless, in order to minimize ventilator-induced lung injury, early extubation to nasal CPAP is a reasonable strategy. **Criteria for extubation to nasal CPAP in the first week of life are:**
- Adequate respiratory drive, *and*
- Mean airway pressure ≤7 cmH$_2$O, *and*
- F$_I$O$_2$ ≤0.35

Nasal CPAP is delivered via a specialized nasal mask or prongs, utilizing a patient-demand flow system. CPAP is administered between 4 and 6 cmH$_2$O. Lower pressures do not maintain lung inflation and higher pressures often cause gastric distension. Limitations to the use of nasal CPAP include hypercarbia, frequent episodes of apnea, gastric distension and breakdown of nasal skin and mucosa from the mask/prongs.

The method and timing of further weaning, from nasal CPAP to supplemental O$_2$ via nasal cannula, varies with gestational age, post-natal age, weight and stability of the individual patient. Some infants require a gradual transition to nasal cannula through "sprinting," a process in which infants are trialed on nasal cannula for a portion of the day and then returned to nasal CPAP. As the infant demonstrates increased tolerance of these trials, the length of these trials is slowly extended.. The time of these trials often coincides with feeds, in order to minimize handling of VLBW infants (*e.g.*, if feedings are q3 hours, trials of nasal cannula are usually increased in 3 hour intervals).

5. Antibiotic therapy: The clinical and radiographic features of pneumonia may be indistinguishable from RDS at birth. As a result, all infants with RDS should have blood cultures and CBC drawn, and should receive empiric antibiotic therapy (Ampicillin and Gentamicin). Generally, antibiotics may be discontinued if the blood culture has no growth after 48 hours, unless prenatal history or clinical scenario warrants extended treatment.

6. Thermoregulation: Careful temperature control is imperative in all VLBW infants and is especially important in infants with RDS to minimize metabolic demands and oxygen consumption. RDS can limit oxygen uptake leading to hypoxia which limits the ability of an infant to increase their metabolic rate when cold stressed, resulting in a fall in body temperature. An incubator or radiant warmer must be utilized to maintain a neutral thermal environment for the infant. For further discussion, see the sections on VLBW Infants (P. 65) and Health Care Maintenance (P. 48).

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