Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), also known as *hyaline membrane disease* (HMD), is the dominant clinical problem and a major cause of morbidity and mortality in the premature neonate. Surfactant deficiency or dysfunction along with structurally and functionally immature lungs contribute to RDS.

Risk Factors

Premature and low-birth-weight infants are at the highest risk for developing RDS, and risk increases with younger gestational age and lower weight. At 23%–25% gestation, infants have approximately a 90% chance of developing RDS. Those delivered at 26–27 weeks gestation, 88%; 28–29 weeks gestation, 74%; and by 30–31 weeks gestation, the risk falls to approximately 50%. Other risk factors include

- male gender
- multiple gestation
- caucasian race
- previous infant with RDS
- perinatal asphyxia
- cesarean section without labor
- maternal diabetes
- antenatal infection such as chorioamnionitis (Newborns who develop RDS after exposure to chorioamnionitis tend to have a more severe course of RDS and more frequently develop bronchopulmonary dysplasia.)
- absence of antenatal steroid administration to the mother.

Factors Associated with Decreased Risk

The risk of neonatal RDS may be reduced in the presence of

- maternal chronic or pregnancy-induced hypertension
- maternal cocaine use
- maternal stress
- corticosteroids and thyroid hormones
- placental insufficiency (stress in the fetus may have the secondary effect of inducing accelerated lung maturation).

Normal Fetal and Neonatal Lung Development

A basic understanding of lung development and maturation will facilitate an understanding of how RDS occurs. Normal lung development can be divided into five stages:

- embryonic stage
- pseudoglandular stage
- canalicular stage
- saccular stage
- alveolar stage.

The Embryonic Stage (Embryonic Weeks 4–7)

The fetal lung bud—consisting of epithelium and surrounding mesenchyme, an endoderm-lined out-pouching of the primitive foregut—is first evident around embryonic day 24–26. During the next 3–5 weeks, the lung bud divides and branches dichotomously, giving rise to the conducting airways (trachea, right and left main bronchi, and segmental bronchi) and five primordial lung lobes (two left and three right). During the initial phase of development, the primitive airways are surrounded by loose mesenchyme supplied by primitive systemic arteries. Near the end of the embryonic period, the primitive systemic vessels are replaced by the pulmonary arteries.

The Pseudoglandular Stage (Embryonic Weeks 6–16)

During this stage, the airways grow to the level of the terminal bronchioles and primitive acini are formed. By the end of the pseudoglandular stage, branching of the large conducting airways is complete.

The Canalicular Stage (Embryonic Weeks 17–27)

During this stage, the blood-gas barrier begins to thin and an immature surfactant-producing system starts to develop, transforming the previable lung into a potentially viable lung. Distal airways develop into definitive primary acini, and the alveolar capillary barrier is formed. True acinus, the gas exchange unit of the lung encompassing a respiratory bronchiole and its associated alveolar ducts and alveoli, do not develop until around 36 weeks gestation. By 20–22 weeks gestation, epithelial differentiation into immature type I and II pneumocytes begins. Type I

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pneumocytes are flat cells lining the alveoli and are necessary for gas exchange. Type II pneumocytes are cuboidal cells responsible for producing surfactant. At this stage, the surfactant components produced by type II cells are detectable in the form of lamellar inclusion bodies. Vascularization of the dense mesenchyme surrounding the airways begins.

The Saccular Stage (Embryonic Weeks 25–38)

During this stage of development, evolution of the relationships between the airspaces, capillaries, and mesenchyme acquire greater significance, and airway walls become increasingly thin, increasing the gas-exchanging surface area. Lamellar bodies containing surfactant and phospholipid in type II pneumocytes increase and mature, and further maturation of type II into type I cells continues. Alveolar ducts, mature cup-shaped alveoli, line the elongated saccules by around 34 weeks gestation.

The Alveolar Stage (Embryonic Week 36–3 Years of Age)

Alveolar formation and maturation continues through this phase of development. At the beginning of the alveolar stage, the walls of the alveoli are thicker than adult alveoli. The double capillary supply persists, as does mesenchymal tissue between the epithelial layers. Apoptosis enables development of a single capillary loop, and the number of type I and II pneumocytes lining alveolar walls increases. There is an overall increase in gas-exchanging surface area. The majority of alveolarization is believed to occur within the first 5–6 months of age, but it continues at a slower rate up to at least 2–3 years of age. Some evidence suggest this stage lasts through 7–8 years of age; others suggest it lasts even later into early adulthood.

Timing of the stages is not definitive, and the stages overlap.

Normal Anatomical and Physiological Features of Newborn Respiratory System

The respiratory system of the healthy term neonate is anatomically and physiologically different from the adult respiratory system. These differences are more profound with younger gestational age. Some of the differences are outlined below.

The head of the neonate is larger in proportion to the body than the adult's head is to the body. The large head size predisposes the neonate to malposition and mechanical occlusion of the airway. Further, neuromuscular development is immature, which limits ability to correct by repositioning. The head is the largest body surface area in the neonate and where heat loss is most abundant. Hypothermia may induce and exacerbate respiratory compromise.

The tongue also is proportionately larger in the neonate, and combined with the large amount of lymphoid tissue in the pharynx, can contribute to airway obstruction.

Neonates prefer to breathe through the nose, but the diameter of the nares is smaller. The small nares can be easily occluded by secretions, inflammation, and devices, which may compromise the newborn respiratory status.

The ribs and sternum are primarily cartilage, the ribs are horizontally oriented, and the muscles are immature and shorter. These differences decrease the ability to lift the ribs during inspiration to increase intrathoracic volume. The diaphragms are inserted horizontally and are flatter than the adult, resulting in an inward movement of the lower ribs during inspiration. Muscle endurance is determined by muscle mass and oxidative capacity of the muscle fibers. Premature infants with respiratory compromise have both decreased muscle mass and are subjected to frequent periods of hypoxemia, which increases the risk of muscle fatigue and respiratory failure.

The airways are smaller both in length and diameter, and they have less smooth muscle than the adult. These features predispose the infant to having "floppy," or more compliant, airways.

The upper airway is significantly different in the infant. The epiglottis is proportionately larger than in the adult, less flexible, and omega shaped. These differences increase the risk of trauma and obstruction. The larynx
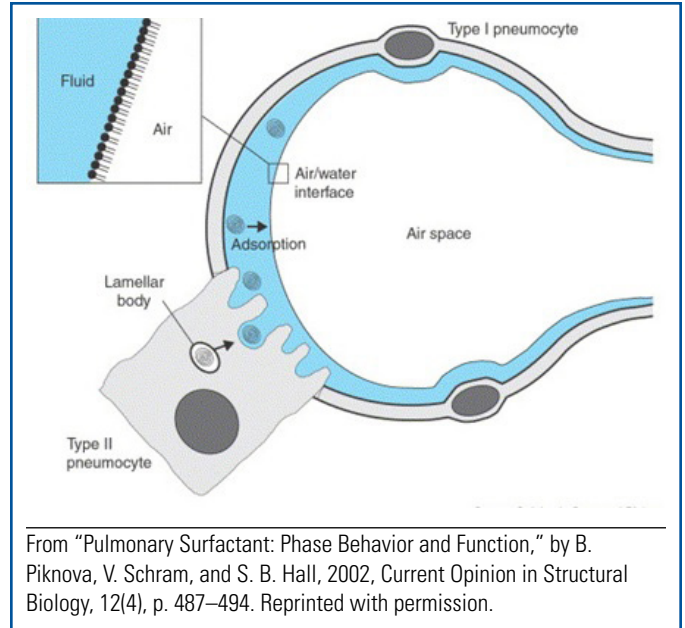
lies higher in the neck in relation to the cervical spine. The cricoid ring is the most narrow point in the trachea, forming the distinct funnel shape of the neonatal trachea. This natural narrowing allows the use of uncuffed endotracheal tubes in neonates.

The alveoli are the gas-exchange units in the lung and comprise the largest surface area of the lungs. The healthy full-term neonate is born with approximately 50 million alveoli with a well-developed microvasculature, whereas an adult has around 300 million alveoli. Premature infants born prior to 24 weeks gestation have just matured beyond the canalicular stage to the beginning of the saccular stage of development. This lung has undifferentiated distal air saccules and a poorly developed microvasculature. The potential gas-exchange surface area increases significantly after 29 weeks gestation.

Surfactant

Surfactant is produced and stored by type II pneumocytes in the distal airway epithelium. The first evidence of cellular differentiation occurs around 22 weeks gestation. Primitive type I and type II pneumocytes are evident at this stage, and primitive lamellar bodies are present. The 22-week fetal lung contains primitive structures and functions to survive outside of the womb, though this capability is limited and most often requires assisted ventilation.

Surfactant is a complex mixture of phospholipids, neutral lipids, and proteins and is a major determinant of alveolar wall surface tension. A thin film is spread at the air-liquid interface of the alveolar surface, thereby lowering the surface tension and preventing alveolar collapse, especially at low alveolar volumes reached at end-expiration. Surfactant produced by the 22- to 24-week fetal lung is functionally immature, and the volume is inadequate. It is not until around 30 weeks gestation that an adequate volume is produced and around 34 weeks before the produced surfactant shows functional maturity.

From "Pulmonary Surfactant: Phase Behavior and Function," by B. Piknova, V. Schram, and S. B. Hall, 2002, *Current Opinion in Structural Biology, 12*(4), p. 487–494. Reprinted with permission.

Surfactant synthesis is a dynamic process that depends on normal pH, temperature, and perfusion, and may be compromised by cold stress, hypovolemia, hypoxia, and acidosis. Exposure to high inspired-oxygen concentrations and the effects of barotrauma and volutrauma from assisted ventilation can trigger the release of proinflammatory cytokines and chemokines and further damage the alveolar epithelial lining, resulting in impaired surfactant synthesis and function. Furthermore, leakage of proteins such as fibrin into the intra-alveolar space aggravates surfactant deficiency by promoting surfactant inactivation.

Pathophysiology

RDS is a state of pulmonary insufficiency that manifests at or shortly after birth. Premature infants are born with underdeveloped, small alveoli that are difficult to inflate and larger, though still immature, alveoli that can easily become over distended. The alveoli that are available for gas exchange do not have the amount of surfactant necessary to maintain alveolar distention at end-expiration, resulting in atelectasis, and inspired air preferentially flows to the larger alveoli, resulting in further over distention. The premature infant is unable to achieve the significant negative inspiratory pressure required to open the atelectatic regions, and the result is significantly increased work of breathing and hypoxemia.

Shear stress caused by repetitive attempts to reopen the collapsed alveoli results in significant damage to the lung epithelium. Increased work of breathing, hypoxia, and atelectasis leads to decreased tidal volumes causing alveolar hypoventilation and hypercapnia. Hypoxia and hypercapnia cause pulmonary vasoconstriction, which increases intrapulmonary resistance and intrapulmonary shunting. Intrapulmonary shunting results in the collapse of arterioles, thus receiving decreased blood flow and resulting in pulmonary hypertension. Prolonged hypoxemia activates anaerobic glycolysis, which produces lactic acid, resulting in lactic acidosis. Alveolar hypoventilation causes a worsening hypercapnia, which results in combined metabolic and respiratory acidosis. The acidosis causes further vasoconstriction, leading to more severe hypoventilation of the lung, intrapulmonary shunting, pulmonary hypertension, and intracardiac shunting through the foramen ovale and ductus arteriosus. Inadequate pulmonary perfusion causes worsening hypoxemia, acidosis, and decreased ability to produce surfactant. Capillary permeability increases, resulting in leakage of plasma proteins. Fibrin deposits accumulate in the air spaces, creating the appearance of hyaline membranes and further interfering with the function of available surfactant.

Clinical Manifestations

Signs and symptoms usually are apparent within minutes of birth, though manifestation may occur over the first few hours of life and can be exacerbated by cold stress or hypoglycemia. Infants presenting with severe respiratory distress or asphyxia require immediate resuscitation. The most striking clinical manifestations include tachypnea or apnea, expiratory grunting, intercostal and subcostal retractions, nasal flaring, poor color, decreased perfusion, and bradycardia. Progressive hypoxemia and dyspnea characterize the natural course. Within the first 6 hours of life, the chest X ray will reveal air-filled bronchi (air bronchograms) silhouetted against lung fields that have a "ground glass" appearance. Without intervention, RDS can progress to death. Uncomplicated or appropriately managed RDS usually peaks within the first 3 days followed by a gradual improvement.

Management

Management optimally begins prenatally, with prevention of preterm birth being the most effective method to prevent RDS. Mothers presenting in preterm labor between 24 and 34 weeks gestation, when labor can be stopped or is not imminent, should receive antenatal glucocorticoids. Glucocorticoids are optimally administered in two doses over 48 hours; however, one dose administered at least 12 hours prior to delivery has been effective in reducing the severity of RDS. Multiple dosing has been associated with adverse effects, though the evidence is unclear, and dosing prior to 24 weeks gestation has not been well studied. Glucocorticoids induce significant and rapid acceleration of lung maturation and stimulation of surfactant production in the fetus. Some evidence shows that glucocorticoids not only reduce the severity of RDS but also may be valuable in reducing the incidence of central nervous system hemorrhage and neonatal mortality. Some research has suggested that although glucocorticoids are effective in accelerating early lung maturation, they may also be associated with abnormal lung development later in neonatal life.

Exogenous surfactant is another major advancement in the care and treatment of infants with RDS. Exogenous surfactant is available in synthetic or purified forms from animal sources, and it is instilled down the endotracheal tube. It is administered either prophylactically or as a rescue measure (there are new delivery methods being

explored that include less invasive surfactant administration). Prophylactic surfactant is ideally administered to the infant in the delivery room or within the first 15–30 minutes of life. The criteria for prophylactic administration varies among institutions and is most often determined by the infant's clinical status and most premature infants included in the selection criteria. Otherwise, for larger premature infants, prophylactic surfactant is administered based on clinical presentation. Repeat dosing is determined by the infant's clinical status, and timing and frequency is based on the manufacturers' guidelines. Immediate improvement in oxygenation and ventilation is common and requires immediate intervention, such as decreasing inspired oxygen concentration, the peak inspiratory pressure (PIP; tidal volume, mean airway pressure), and possibly the positive-end expiratory pressure (PEEP) to avoid over distention and oxidative damage to the fragile lung tissue. Rescue surfactant is administered to infants who exhibit progressively worsening clinical symptoms, increasing oxygen requirements, or worsening blood gases.

Current evidence promotes treatment methods directed at protecting the fragile lung. Oxidative damage has been well researched, and studies show that administering high concentrations of oxygen in the delivery room induces oxidative lung damage that may be irreversible. Further, resuscitation provided via a T-piece device that allows control of PIP and delivering a constant PEEP improves lung volumes, facilitates functional residual capacity, and reduces the incidence of volutrauma and barotrauma. Stable premature infants who do not meet criteria for prophylactic surfactant administration may be placed on continuous positive airway pressure (CPAP) and monitored closely. Some infants who require surfactant (prophylaxis or rescue) are intubated, given surfactant, and immediately extubated to CPAP. Volume ventilation provides a more physiologic method of ventilation and high-frequency ventilation provides a gentler method of ventilation.

Complications

Significant complications found in survivors of RDS include

- intracranial hemorrhage
- pulmonary hemorrhage
- sepsis
- necrotizing enterocolitis
- bronchopulmonary dysplasia.

It is unknown if the complications are the result of the underlying pathophysiology of RDS, administered treatments, or underlying prematurity.

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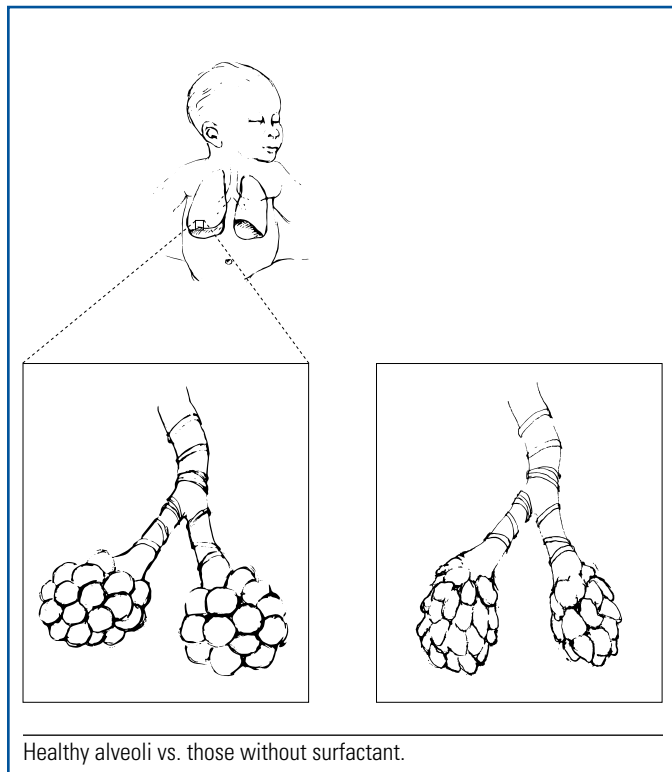
Respiratory Distress Syndrome: Information for Parents

Respiratory distress syndrome (RDS) also is known as hyaline membrane disease (HMD). This condition makes it difficult for the baby to breathe on his or her own.

RDS happens in babies whose lungs have not yet fully developed. It is caused when the baby does not have a slippery, protective substance called *surfactant* in the lungs. Surfactant helps the lungs inflate with air and then keeps them from collapsing when the baby exhales. Surfactant is a normal substance found in fully developed lungs.

The earlier the baby is born, the less developed the lungs are and the higher the chance of developing RDS. RDS is most commonly seen in premature infants born before 30 weeks gestation. It is very rare in full-term babies.

Healthy alveoli vs. those without surfactant.

Other things can increase the risk of the baby developing respiratory distress syndrome:
- a brother or sister who had RDS
- when the mother has diabetes (high blood sugar levels) or an infection (chorioamnionitis)

- cesarean section, especially when mother has not experienced labor
- complications that decrease blood flow to the baby before he or she is born:
  - problems with the placenta
  - problems with the umbilical cord
  - a mother who smokes
- multiples in pregnancy (twins/triplets, etc.); the second and third babies are at higher risk
- quick labor (less than 3 hours).

The symptoms usually appear within minutes of birth, but sometimes they do not appear for several hours. Some of the symptoms include
- bluish color of the skin and mucus membranes (cyanosis)
- brief or prolonged periods where the baby stops breathing (apnea)
- a whining or grunting sound when the baby exhales
- nose "spreads out" when the baby inhales (nasal flaring)
- agitated or very weak and limp baby
- shallow and/or rapid breathing
- difficult breathing
- chest that appears to "sink in" with breathing (retractions).

Babies with the worst symptoms appearing in the delivery room will have a breathing tube placed; your baby may receive a form of surfactant (the slippery substance his or her lungs did not produce) down the breathing tube into the lungs to help him or her breathe more easily. Your baby may require more of the surfactant later. Some babies need only one dose, and other babies need as many as four doses. The breathing machine allows the baby to rest while the lungs have a chance to grow and recover.

Babies with less severe symptoms receive help breathing from nasal continuous positive airway pressure (CPAP). This type of support gives pressurized air through the

nose and helps the baby take a deep breath and keep the lungs inflated.

Baby on nasal CPAP. Courtesy of Hospital International.

The neonatal intensive care unit (NICU) staff will watch closely to make sure your baby rests and continues to breathe easily. If your baby needs more help breathing, he or she may need to have a breathing tube placed. Your baby may get a dose (or more) of surfactant.

Your baby's healthcare team usually knows within a few hours if more help to breathe is necessary. The signs and symptoms they look for are
• low blood oxygen levels (desaturations or blood gases)
  – requires more oxygen
• difficulty breathing (retractions, grunting, nasal flaring)
  – requires more pressure from the nasal CPAP or ventilator
• worsening apnea (more episodes, longer episodes, or more effort to stimulate the baby to breathe again).

Other treatments that may be used include
• high-frequency ventilation
  – a breathing machine that breathes very fast but may be less harmful to the fragile lungs
• medications to help the baby breathe easier
  – caffeine or theophylline stimulates the baby to breathe

– lasix (furosemide) or other diuretics to help get rid of extra fluid
– blood pressure support medications.

Babies with RDS have to be monitored very closely. Your baby may need X rays and small amounts of blood drawn to test his or her oxygen levels.

It is very important that all babies with RDS receive excellent supportive care. The following will help to decrease how much oxygen your baby needs:
• dim lighting, quiet room, and few disturbances
• gentle handling
• maintaining ideal body temperature.

Babies with RDS are too sick to eat from a bottle, so they receive nutrition through the IV fluids we give. We may try to feed your baby through a tube inserted into the nose or mouth that goes down into the stomach. At first the amount of food will be very small. Breast milk has the best nutrients and antibodies for your baby. Breast milk will help your baby recover better.

When RDS is the only problem and your baby responds well to the treatments, he or she will start to recover within about 3 days. The full recovery usually takes about 7–10 days, but sometimes a little longer.

Some of the complications associated with RDS, prematurity, or the treatments are
• chronic lung disease, also called bronchopulmonary dysplasia
• bleeding in the lungs, head, or brain
• higher risk of developing an infection
• pneumothorax or other air leaks
  – *Pneumothorax* is when air is found in the chest but outside of the lung.
• necrotizing enterocolitis
  – an infection in the bowel
• patent ductus arteriosus
  – A blood vessel in the heart that is normally open before the baby is born but closes after birth either stays open or reopens after birth.

   Diagnoses