Respiratory Distress Syndrome (RDS), also known as "Hyaline membrane disease", is caused by the deficiency of lung surfactant in a pre-term infant due to the immaturity of the lungs. The risk of RDS is inversely related to the gestational age, and, most commonly occurs in infants less than 28 weeks of gestational age. Neonatal respiratory distress syndrome is associated with high morbidity and mortality in pre-term infants and considered one of the most common causes of neonatal death. Respiratory distress syndrome should be differentiated from the other causes of respiratory distress after birth, which will be discussed in details in this article.

Etiology and Pathophysiology of IRDS

Reviewing normal lung development is important for understanding the pathophysiology of neonatal respiratory distress syndrome.

During intrauterine development, fetal lungs are not functional and filled with fluid; the fetus receives oxygen through the placenta. Fetal lungs start to produce the surfactant during the third trimester of the pregnancy. It reduces tension within the alveoli, thereby preventing their collapse at the end of the expiration that may result in atelectasis, and facilitating the alveolar expansion.
Surfactant production

- It is synthesized by the alveolar type II cells by 20 weeks of gestation
- It appears in the amniotic fluid between 28 and 32 weeks
- Mature levels are usually present after 35 weeks

The major constituents of surfactant are:

- Dipalmitoyl phosphatidylcholine (lecithin)
- Apoproteins (surfactant proteins SP-A, -B, -C, -D)
- Cholesterol.

Phosphatidylglycerol:

The phosphatidylglycerol level is a marker of fetal lung maturity. Immature lungs contain more phosphatidylinositol than phosphatidylglycerol. The phosphatidylglycerol level increases after 35 weeks of gestation.

Surfactant synthesis depends on gestational age, pH, temperature, and perfusion:

- **Gestational age**: The earlier the gestational age (prematurity), the greater the risk of RDS
- **pH**: Any clinical condition causes fetal acidosis and may result in diminished surfactant synthesis
- **Temperature**: Cold stress can suppress surfactant synthesis
- **Perfusion**: Intrapartum asphyxia, hypovolemia, or hypotension can suppress surfactant synthesis

The primary problem of Respiratory Distress Syndrome (RDS) is surfactant deficiency in the premature lungs, which results in higher surface tension. Thus, greater pressure is required to expand the alveoli, and small airways lead to lung instability at end-expiration with low lung volume and decreased compliance. These changes may result in the collapse of portions of the lungs (atelectasis) leading to a mismatch between ventilation and perfusion, which causes hypoxia, hypercapnia, and acidosis.

The combination of hypoxia, hypercapnia, and acidosis may result in pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus → thus, the pulmonary blood flow is decreased, resulting in ischemia of surfactant-producing alveoli and the alveolar bed. The subsequent effusion of proteinaceous material into the alveolar spaces results in pulmonary edema and increased airway resistance.

Risk Factors of IRDS

- **Prematurity**: The smaller the gestational age, the higher the incidence of RDS
- **Maternal Diabetes**: Maternal hyperglycemia causes fetal hyperinsulinemia, which antagonizes cortisol action; therefore, it delays surfactant production in the lungs
- **Cesarean section (C.S) without labor**: A lack of stressful delivery results in reduced fetal cortisone production
- **Perinatal asphyxia**: Due to hypoxemic injury
- **Male gender**
Clinical Manifestations of IRDS

The clinical manifestations arise mainly from abnormal pulmonary function and hypoxemia.

Symptoms of neonatal respiratory distress syndrome

RDS starts within minutes or hours after birth and becomes progressively worse over the first 48 - 72 hours of life. The affected infants are typically premature and show signs of respiratory distress:

- Tachypnea
- Nasal flaring
- Expiratory grunting, which results from expiration against a partially closed glottis
- Cyanosis
- Breath sounds may be normal or diminished with a harsh, tubular quality
- Bilateral fine basal rales

Course of RDS

Uncomplicated RDS typically progresses for 48 - 72 hours and can be followed by increased endogenous production of surfactant. Respiratory distress normally resolves by one week of age. Treatment with exogenous surfactant improves the course of the disease and leads to a resolution of symptoms.

Severe RDS or those inadequately treated may develop:

- Hypotension
- Cyanosis
- Increased pallor
- Grunting decreases or disappears
- Mixed respiratory-metabolic acidosis
- Apnea and irregular respirations which indicate fatigability

Complications of neonatal respiratory distress syndrome
Respiratory failure

- Alveolar air leaks (interstitial emphysema, pneumothorax)
- Pulmonary hemorrhage
- Intraventricular hemorrhage

Diagnosis of IRDS

Diagnosis of neonatal respiratory distress syndrome (RDS) is based mainly on the previously mentioned clinical picture of a premature infant, in conjunction with:

Characteristic chest x-ray findings in RDS

- Diffuse reticulogranular pattern (ground glass appearance)
- Air bronchograms: Outline of air-filled large airways against opaque lungs

They are often more prominent early in the left lower lobe because of the superimposition of the cardiac shadow.

Arterial Blood Gas (ABG) in RDS

- Typically shows hypoxemia which response to oxygen supplementation
- The disease worsens, hypercapnia develops
- Metabolic acidosis

Differential Diagnosis of Dyspnea after Birth

Transient tachypnea

**Symptoms:**

Usually follows an uneventful, normal term vaginal or cesarean delivery with early onset of tachypnea, sometimes with retractions or expiratory grunting. Cyanosis is a typical sign that is relieved by minimal oxygen.
Examination:

Lungs usually clear without rales or rhonchi

**Chest X-ray** shows:

1. Prominent pulmonary vascular markings
2. Fluid lines in the fissures
3. Over aeration
4. Flat diaphragm
5. Pleural fluid

Transient = Hypoxemia, hypercapnia, acidosis are uncommon

**Persistent pulmonary hypertension of the newborn (PPHN)**

Persistence of the fetal circulatory pattern of right-to-left shunting through the POA and foramen ovale after birth is due to very high pulmonary vascular resistance. The condition should be suspected in all term and post-term infants with cyanosis who are unresponsive to 100% oxygen, with or without fetal distress.

**Chest X-ray:**

- May be normal or
- May show parenchymal opacification in the chest, depending on etiology

**Meconium aspiration**

This condition can occur in term or post-term infants, either in utero or more often with the first breath. Thick, particulate meconium is aspirated into the lungs, resulting in:

- Small airway obstruction and consequent respiratory distress, presenting
within the first hour of birth
- Partial obstruction of some airways, which may lead to pneumothorax or pneumomediastinum

**Chest X-ray:**
- Patchy infiltrates with coarse streaking of both lung fields
- Increase anteroposterior diameter
- Flattening of the diaphragm

**Choanal Atresia**

This is the most common nasal malformation. It may be isolated or part of a dysmorphic syndrome. Infants with choanal atresia present with cyclic cyanosis that is aggravated by feeding and relieved by crying.

**Symptom severity** depends on:
- The infant's ability to breathe through the mouth
- Whether one or both choanae are obstructed
- Unilateral choanal atresia may remain undiagnosed until the infant develops an upper respiratory infection
- Failure to pass a catheter through the nose 3 - 4 cm into the oropharynx indicates the diagnosis
- **Investigations:** Diagnosis is confirmed by a CT scan with intranasal contrast, which shows narrowing at the level of the pterygoid plate
Definitive treatment:

- The first step in management consists of placing oral airway + lavage feeding
- Repairing the obstruction with surgery or endoscopy

Congenital Diaphragmatic Hernia

Antenatal history is significant for polyhydramnios in the mother.

Symptoms: Immediately develops a bluish discoloration of the extremities soon after birth, respiratory distress.

Examination:

- Tachypnoea and nasal grunting
- Inspection: Abdomen has a scaphoid shape
- Auscultation: Poor air entry on the left with a shift of cardiac sounds to the right

X-ray shows:

- Air or fluid-filled bowel loops in the hemithorax
- The shift of cardiac shadow to the opposite side
- Placement of orogastric tube before chest X-Ray helps determine the position of the stomach

Management: If the infant has a CDH, or if the diagnosis is suspected in the delivery room:

- First step: Immediate placement of orogastric tube and connecting it to continuous suction, to prevent bowel distension and further lung compression
Endotracheal intubation and mechanical ventilation are also priorities for severe CDH

⇒ CDH is sometimes associated with primary pulmonary hypertension of the newborn (PPHN):

- Continuous pulse oximetry is valuable in the diagnosis and management of PPHN
- If PPHN is present with the right to left ductal shunting, then PaO2 may be higher from a preductal (right-hand) sampling site
- Cardiac ultrasonography can be performed to rule out congenital heart diseases

Management of IRDS

Prevention of neonatal respiratory distress syndrome

As respiratory distress syndrome is a disease of prematurity, the most effective preventive method is to avoid pre-term labor. However, if the pre-term labor can’t be avoided, RDS can be prevented, or its severity decreased by the following interventions:

1. **Antenatal corticosteroids therapy:**
   - Steroid enhances surfactant synthesis and releases and accelerates lung maturity
   - Indications: All pregnant women at risk of pre-term labor, or below 34 weeks
   - Dose: Betamethasone 12mg/IM, two doses 24 hours apart

2. **Exogenous surfactant replacement therapy:**
   Several studies have revealed the benefits of exogenous post-natal surfactant administration in preterm infants born < 30 weeks gestation.

3. **Continuous positive airway pressure (CPAP):**
   - Indications:
     - Premature infants at risk (e.g., low birth weight infants, born at or below 28 weeks gestation)
     - Already established RDS but without respiratory failure
   
   CPAP is an alternative to endotracheal intubation or mechanical ventilation to prevent the development of atelectasis.

Treatment of neonatal respiratory distress syndrome

**General Supportive Measures:**
Early supportive measures aim to control inadequate oxygen and carbon dioxide exchange, metabolic acidosis, and circulatory insufficiency.

**Thermal regulation:**
Avoid neonatal hypothermia by placing the infant in an isolette or radiant warmer and maintaining the core temperature between 36.5 and 37°C.
Fluid Supply:
Fluids should be administered with care because the kidneys have limited concentrating abilities. Large volumes of fluid may increase the risk of patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC).

Nutrition:
Early nutrition is important and should meet the infant’s metabolic needs.

Cardiovascular Support:
A premature infant’s blood pressure should be monitored, and hypotension should be treated with:

- Normal saline (with caution)
- Vasopressors
- Stress doses of hydrocortisone (in persistent hypotension)

Specific Interventions:
The specific interventions for premature infants are based mainly on:

a. Gestational age
b. Respiratory status within the first hour of delivery

- **Humidified oxygen** should be provided in low concentrations to keep PaO$_2$ between 50 and 70 mm Hg (85 – 95% saturation) to maintain tissue oxygenation and avoid the risk of oxygen toxicity; pH should be maintained > 7.25

- **CPAP at a pressure of 5-10 cm H$_2$O** should be provided if initial oxygen supply with the concentration greater than 60% cannot maintain PaO$_2$ above 50 mmHg

- **Assisted Mechanical Ventilation is indicated** for respiratory failure (Pco$_2$ > 60 mm Hg, pH < 7.20, and PaO$_2$ < 50 mm Hg despite 100% oxygen)

Note: Exogenous surfactant can be administered repeatedly in patients receiving oxygen therapy, endotracheal intubation, and mechanical ventilation during RDS.
References


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