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

Discussing the normal lung development is important to understand the pathophysiology of neonatal respiratory distress syndrome.

Fetal lungs during the intrauterine life are not functional and filled with fluid, where the oxygen is delivered to the fetus through the placenta. Fetal lungs start to produce the surfactant during the third trimester of the pregnancy. The surfactant reduces tension within the alveoli, thereby preventing their collapse at the end of the expiration which may result in atelectasis, and facilitating the alveolar expansion.
Surfactant production

- It’s synthesized by the alveolar type II cells by **20 weeks of gestation**.
- It appears in 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:

Phosphatidylglycerol level begins to rise in amniotic fluid **after 35 weeks of gestation** and is used as a marker for fetal lung maturity. Instead of high levels of phosphatidylglycerol in mature lungs, immature lungs contain a larger amount of phosphatidylinositol than a smaller amount of phosphatidylglycerol.

Synthesis of the surfactant depends on **gestational age, pH, temperature and perfusion**:

- **Gestational age:** The earlier gestational age (prematurity), the more risk of RDS.
- **pH:** Any clinical condition causes fetal acidosis and may result in diminished surfactant synthesis.
- **Temperatures:** Such as 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 leading to instability of the lung at end-expiration, 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 with subsequent effusion of proteinaceous material into the alveolar spaces, resulting in pulmonary edema and increased airway resistance.

Risk Factors of IRDS

- **Prematurity:** The smaller the gestational age, the higher incidence of RDS.
- **Maternal Diabetes:** Maternal hyperglycemia causes fetal hyperinsulinemia which antagonizes the action of cortisol; therefore delays the maturation of 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 the hypoxemic injury if the alveolar cells type 2.
- **Male gender.**
Clinical Manifestations of IRDS

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

By auscultation:

- Breath sounds may be normal or diminished with a harsh tubular quality.
- Bilateral fine basal rales.

Course of RDS

Uncomplicated RDS typically progressed for 48 - 72 hours, can be followed by increased endogenous production of surfactant and resolution of the respiratory distress 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
- Pallor increase
- Grunting decrease or disappear
- 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 superimposition of the cardiac shadow.

Arterial Blood Gas (ABG) in RDS

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

Differential Diagnosis of Dyspnea after Birth

Transient tachypnea

Symptoms:

Usually follows an uneventful normal term vaginal delivery or cesarean delivery with early onset of tachypnea, sometimes with retractions or expiratory grunting + typically, cyanosis 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.

Clinically:
Should be suspected in all term and post-term infants with cyanosis 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

Occurs in term or post-term infants

Occurs either in utero or more often with the first breath, thick and particulate
**meconium** is aspirated into the lungs, resulting in:

- Small airway obstruction and consequent → respiratory distress that presents within the **first hour of birth**
- Partial obstruction of some airways → may lead to pneumothorax or pneumomediastinum

**Chest X-ray:**

- Patchy infiltrates, coarse streaking of both lung fields
- Increase anteroposterior diameter
- Flattening of the diaphragm

**Choanal Atresia**

It is the **most common nasal malformation**. It may be isolated or part of a dysmorphic syndrome. Suspect choanal atresia in who presents with **cyclic cyanosis that is aggravated by feeding and relieved by crying**.

**The severity** of symptoms depends on:

- The ability of the infant to **breathe through the mouth**.
- Whether **one or both choanae** are obstructed.
- **Unilateral choanal atresia** may remain undiagnosed until the infant develops a **first upper respiratory infection**.
- Failure to pass a catheter through the nose 3 - 4 cm into the oropharynx is suggestive of 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 develop bluish discoloration of extremities soon after birth, respiratory distress.

Examination:

- Tachypnoea and nasal grunting.
- Inspection: Abdomen has 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 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 the respiratory distress syndrome is a disease of prematurity, the most effective preventive method is to avoid the 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 release and accelerates lung maturity.
   - Indications: All pregnant women at risk of pre-term labor, or below 34 weeks.
   - Dose: Betamethazone 12mg/IM, two doses 24 hours apart.

2. **Exogenous surfactant replacement therapy:**
   
   Several studies have revealed 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 considered 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 the inadequate exchange between the oxygen and carbon dioxide exchange, metabolic acidosis and circulatory insufficiency.

**Thermal regulation:**

Avoid the neonatal hypothermia by placing the infant in an isolette or radiant warmer and core temperature maintained between 36.5 and 37°C.
Fluid Supply:
You should be careful with the administration of fluid, as the kidneys have limited concentrating abilities and administration of 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 metabolic needs of the infants.

Cardiovascular Support:
Blood pressure of a premature infant 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 to premature infants are based mainly on:

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

- **Humidified oxygen** should be provided in low concentration to keep Pao$_2$ between 50 and 70 mm Hg (85 - 95% saturation) to maintain tissue oxygenation and avoiding 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% couldn't maintain Pao$_2$ above 50 mmHg.

- **Assisted Mechanical Ventilation** is indicated if a respiratory failure occurred (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.
Review Questions

The answers are below the references.

1. The incidence of respiratory distress syndrome (RDS) increases with all of the following risk factors except:
   A. Maternal diabetes.
   B. Prematurity.
   C. Caesarean section delivery.
   D. Female gender.

2. The main pathophysiological cause of neonatal respiratory distress syndrome is...
   A. ...surfactant deficiency.
   B. ...hypoplasia of the lungs.
   C. ...incomplete development of the alveoli.
   D. ...alveoli that are abnormally filled with fluid.

3. A premature infant was born at 28 weeks of gestation, and, after 3 hours of birth, he developed tachypnea and intercostals retractions. An X-Ray was asked and a diagnosis of respiratory distress syndrome (RDS) was made and, after 100% oxygen therapy, the APG of the infant showed: Pco2 > 60 mm Hg, pH < 7.20, and Pao2 < 50 mm Hg. The most appropriate next step in management is:
   A. Give higher concentrations of oxygen.
   B. Start Continuous Positive Airways Pressure (CPAP).
   C. Start Assisted Mechanical Ventilation.
   D. Administrated exogenous surfactant.

References


Correct answers: 1D, 2A, 3C