

## PREVENTION OF NEONATAL RESPIRATORY DISTRESS SYNDROME

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### Abstract

Respiratory distress syndrome (RDS) is one of the most frequent respiratory diseases and is a leading cause of neonatal morbidity and mortality. RDS is also known as hyaline membrane disease. Preterm birth is the most important risk factor in the development of respiratory distress syndrome. The main cause of severe respiratory syndrome is lung surfactant deficiency. Inadequate surfactant production leads to diffuse alveolar atelectasis, edema, cell injury and the decrease of lung compliance.

Prenatal diagnosis to identify children at risk, prevention of disease by antenatal administration of glucocorticoids, improving perinatal and neonatal care, advances in respiratory support and surfactant administration, have reduced mortality associated with respiratory distress syndrome.

Despite recent advances in perinatal management of severe neonatal respiratory distress syndrome, controversies still exist. (1,3,9)

**Keywords:** neonatal respiratory distress syndrome, surfactant therapy, prevention, antenatal steroids, preterm birth

### Introduction

Adequate pulmonary function is essential for the newborn survival. For this reason, lung development during perinatal period was a vast area of research. Intrauterine development of respiratory system begins from a lung bud. Then he divides, branch out and penetrate the mesenchyme, progressing to the periphery. The lung development goes through five stages:

- I. Embryonic stage (5 weeks post conception)- proximal airway development
- II. Pseudoglandular stage (5-16 weeks of gestation)- lower airway development

- III. Canalicular stage (17-24 weeks)- vascular canals multiply to form the alveolar-capillary respiratory membrane
- IV. Saccular stage (24-37 weeks)- characterised by dilatation of terminal respiratory units into alveolar saccules and ducts
- V. Alveolar stage (37 weeks to 3 years postnatally)- formation of secondary alveolar septa that partition the terminal ducts and saccules into mature alveoli (4,10)

The lungs have two types of circulation. Bronchial arteries are part of systemic circulation and the pulmonary arteries participate to the pulmonary gas exchange. Proper lung function requires anatomical integrity and maturity respiratory control. In fetal life, the lung is only 10% oxygenated. It is filled with fluid, which at birth is discharged and replaced with air, to ensure and maintain residual capacity. During the labour, the compression performed on the thorax facilitates the removal of lung fluid. The intraalveolar lung fluid moves into the interstitium and is partially absorbed by the capillaries. Pulmonary surfactant coats the alveoli and lowers the surface tension, facilitating lung expansion. Respiratory distress syndrome (RDS) represent an important pulmonary pathology. It occurs mainly in premature infants, due to pulmonary immaturity and lung surfactant deficiency. (4,5,10)

### Incidence

It is inversely related to gestational age:

- thus 80% at 24 weeks of gestation;
- 70% at 28 weeks of gestation;
- 25% at 32 weeks of gestation;
- 5% at 36 weeks of gestation.

Risk factors for RDS (2,11) are shown in table 1.

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Table 1. Risk factors for RDS.

Increased risk	Decreased risk
<ul style="list-style-type: none"> <li>• Prematurity</li> <li>• Male gender</li> <li>• Familial predisposition</li> <li>• Cesarean section without labor</li> <li>• Perinatal asphyxia(Apgar score &lt;4)</li> <li>• Chorioamnionitis</li> <li>• Multiple pregnancy</li> <li>• Matern diabetes</li> <li>• Early clamping of the umbilical cord</li> <li>• Hypothyroidism</li> <li>• Hypothermia</li> <li>• Maternal malnutrition</li> <li>• Non-immune hydrops fetalis</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic intra-uterine stress</li> <li>• Prolonged rupture of membranes</li> <li>• Maternal hypertension or toxemia</li> <li>• Maternal use of narcotics/cocaine</li> <li>• Intrauterine growth retardation or small for gestational age</li> <li>• Antenatal glucocorticoids</li> <li>• Tocolytic agents</li> <li>• Hemolytic disease of the newborn</li> <li>• Black race</li> </ul>

Pathophysiology

The primary cause of respiratory distress syndrome is inadequate pulmonary surfactant (production or decreased secretion). The surfactant is a lipo-protein complex secreted by the type II pneumocytes. It is found in fetal lung at 20 weeks of gestation , but in the alveoli is found much later. Surfactant is also found in the amniotic fluid at 28-32 weeks of gestation. After 34-35 weeks of gestation, the pulmonary surfactant has appropriate levels.

Surfactant has a number of properties who has the purpose to reduce surface tension and the tendency to

collapse of the alveoly. This properties are: increase pulmonary compliance, alveolar stabilization and pressure drop necessary to maintain alveoli open. The structurally immature and surfactant deficient lung has low compliance and a tendency to atelectasis. Intraalveolar pressure drop, alveolar collapse, altered ventilation/perfusion ratio, intrapulmonary shunts, decreased pulmonary compliance and pulmonary resistance growth, leads to the appearance of hypoxia, hypercarbia and acidosis (figure 1).(5,11)

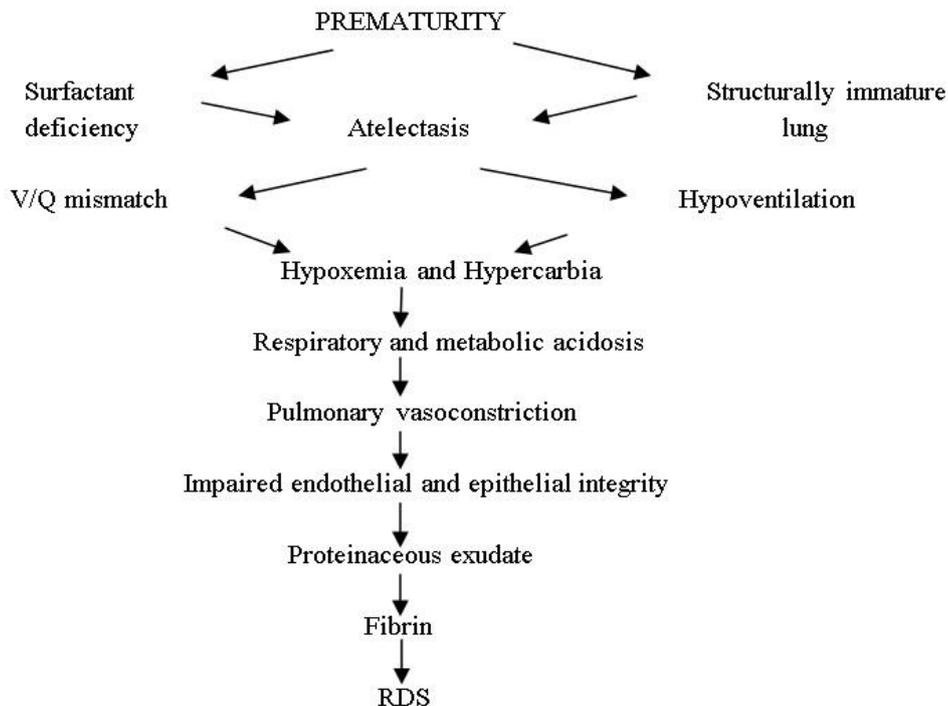


Fig. 1. Pathophysiology of RDS.

Pathological anatomy

Macroscopically the lungs appear congested, atelectatic, with a dark red color. Microscopically is seen diffuse alveolar atelectasis, pulmonary edema and dilated alveolar capillaries and lymphatics. In the alveoli is observed hyaline membrane homogeneous or granular. Amniotic cells, intraalveolar hemorrhage and interstitial

emphysema are also found. Hyaline membranes rarely appear before 6-8 hours from birth. (4,5,10)

Clinical features

Signs of RDS appear immediately after birth or within 4 hours. Respiratory distress severity is assessed after Silverman Score (table 2).(2)

Table 2. Signs of RDS.

Silverman Score	Chest movements	Xiphoid Retraction	Intercostal Retraction	Expiratory Grunt	Nasal flaring
Score 0	Equal	None	None	None	None
Score 1	Respiratory lag	Minimal	Minimal	Audible with stethoscope	Minimal
Score 2	Seesaw respiration	Marked	Marked	Audible	Marked

Silverman Score interpretation :

- score 0 - indicates no respiratory distress
- score 4-6 – indicates moderate respiratory distress
- score 7-10 – indicates severe respiratory distress

Respiratory distress syndrome is characterized by one or more of the following: nasal flaring, chest retractions, tachypnea, grunting and cyanosis. Tachypnea represent respiratory rate over 60/min. It is due to an attempt to increase minute ventilation to compensate for a decreased tidal volume and increased dead space. Retractions occurs as the infant is forced to generate a high intrathoracic pressure to expand the poorly compliant lungs. Grunting represent the compensation mechanism against alveolar collapse. Grunting results from the partial closure of the glottis to maintain the alveolar volume. Other clinical features may include: oliguria, hypothermia, hypotension, hypotonia and acidosis. (3,4,5,12)

Investigations

- *Antenatal*: determination of lecithin/sphingomyelin ratio in the amniotic fluid:

- normal is >2 (except newborns from diabetic mother where a ratio > 2 can mean hyaline membrane disease)
- L/S ratio =1,5 can signify high risk for hyaline membrane disease.

- *Postnatal*:

I. Noninvasive monitoring:

- SaHbO<sub>2</sub> – normal = 92-98%  
– < 88% indicate the need for assisted ventilation
- Transcutaneous blood gas: normal parameters PaO<sub>2</sub> arterial = 55-80 mmHg, PaCO<sub>2</sub> arterial = 40-50 mmHg, pH arterial = 7,30-7,40.
- Blood pressure: try to maintain systolic blood pressure > 60mmHg and/or medium blood pressure (MAP) >30 mmHg.

II. Monitoring acid-base balance and blood gases.

Initially laboratory changes are characterized by: hypoxemia, hypercarbia, acidosis (first respiratory, then metabolic or mixed – it is desired to maintain pH value between 7,30-7,40).

III. Chest x-ray highlights low lung volumes and a bilateral, reticular granular pattern with superimposed air bronchograms. In more severe cases there is complete "white out" of the lung fields.

IV. ECG exam is required to specify cardiac impairment.

V. Transfontanelar ultrasound exam – required to specify the neurological complications.

VI. Blood exam: Ht, Hb, urea, creatinine, glucose.

VII. Blood culture – for infections risk assessment.(1,2,5)

Management

The treatment purpose of child with respiratory distress syndrome is to avoid hypoxemia, acidosis, fluid overloading in an attempt to avoid hypovolemia and hypotension and also minimizing lung injury. The most important advances in prevention and treatment of respiratory distress syndrome are:

- a) antenatal glucocorticoids,
- b) surfactant administration,
- c) continuous positive airway pressure (CPAP).

These have decreased morbidity and mortality from respiratory distress syndrome.(7,8,9)

Antenatal glucocorticoids accelerate fetal lung maturity. This process is made by increasing formation and surfactant secretion, and also maturing the lung morphologically. Prenatal steroids decrease the risk of RDS and additionally decrease the risk of intraventricular haemorrhage. Antenatal glucocorticoids are recommended in all pregnancies with threatened preterm labour below 34 weeks of gestation. Administration of corticosteroids, like betamethasone 12 mg every 24 hours, 2 doses 48 hours before birth or dexamethasone 6 mg, 4 administrations every 12 hours, 48 hours before birth, to mothers at least 24-48 hours before premature birth, decreases the incidence and

severity of the RDS. Glucocorticoids also reduces the incidence of other complications of prematurity, such as intraventricular hemorrhage, pneumothorax, patent ductus arteriosus, ulceronecrotic enterocolitis. (8,9,11)

**Surfactant therapy:** Exogenous natural surfactant (porcine/bovine source) or synthetic (table 3), may be used prophylactic to the preterm infant (< 32 weeks of gestation) in the delivery room in the first minutes after birth, as soon as the infant has been stabilized. The benefit of this action is to replace the surfactant before RDS develops and to avoid or ameliorate lung injury. The administration of surfactant is curative to infants who already developed RDS and require mechanical ventilation and supplemental O<sub>2</sub>.

Administration of exogenous surfactant to infants who require oxygen concentration greater than 30% and mechanical ventilation for the treatment of hyaline membrane disease improved the survival of this babies and reduced the incidence of immediate pulmonary complications (interstitial emphysema, pneumothorax). But, unfortunately, did not reduce the incidence of bronchopulmonary dysplasia. Several studies have shown that two doses, 12 hours apart, may be more effective than single dose therapy. More than 2 doses is rarely required and is rarely effective. (2,9)

Table 3. Surfactant preparations licensed in Europe in 2013.(9)

Generic name	Trade name	Source	Manufacturer	Dose(volume)
Beractant	Survanta®	bovine	Ross Laboratories (USA)	100mg/kg/dose(4ml/kg)
Bovactant	Alveofact®	bovine	Lyomark Pharma(Germany)	50mg/kg/dose (1,2ml/kg)
Poractant alfa	Curosurf®	porcine	Chiesi Farmaceutici(Italy)	100-200mg/kg/dose (1,25-2,5ml/kg)

**Nasal CPAP:** Invasive mechanical ventilation of an immature lung has long-term side effects and should be avoided as much as possible. Prophylactic CPAP after birth is recommended to all preterm infants with less than 30 weeks of gestation who are breathing spontaneously and no clinical criteria for intubation and mechanical ventilation, until their clinical condition can be assessed. CPAP help prevent alveolar and airway collapse.(9,11)

**Mechanical ventilation:** All neonates with respiratory distress syndrome should be intubated and mechanically ventilated, in order to reduce mortality. Mechanical ventilation is recommended to all preterm babies with: RDS and severe apnea who do not respond to CPAP, PaCO<sub>2</sub> >55-60 mmHg, pH <7,25, gestational age less than 27 weeks and no antenatal glucocorticoids. Duration of mechanical ventilation should be limited as much as possible, since all modes of ventilation can induce lung tissue damage.(9)

**Oxygen therapy after stabilization:** At preterm babies who require oxygen therapy, oxygen saturation must be maintained at values between 85-93%. Higher O<sub>2</sub> concentrations will increase the risk for retinopathy of prematurity, chronic lung disease, brain injury, ulceronecrotic enterocolitis. Administered oxygen must be humidified and heated, because dry and cold gas causes heat loss and airways damage.

**Antibiotic therapy :** Antibiotics are often started in babies with RDS, until laboratory results from blood culture arrives. A common regimen includes Ampicillin with Gentamicin, or cephalosporin with amikacin or metilmicin.(9)

**Thermoregulation:** Temperature control (36,5-37,5°C) is important to minimize metabolic demands and oxygen consumption. An incubator or radiant warmer must be utilized to maintain a neutral thermal environment for the infant.

Without complications respiratory distress syndrome to premature infants often get worse in 2-4 days from birth, with a slow improvement after. Some babies with RDS dies, although this is rare in the first day of life. If it occurs, is usually between 2 and 7 days. Thus, to a birth weight below 501 g survival rate is 10% and the risk of developing bronchopulmonary dysplasia is 100%. If the weight at birth is between 1001-1500 g, survival rate is approximately 96% and the risk of developing bronchopulmonary dysplasia decreases significantly.

The aim of management of RDS is to provide intervention that will maximize survival while minimizing potential adverse effects.

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