

Respiratory Distress Syndrome (Hyaline Membrane Disease)

INCIDENCE

RDS occurs primarily in premature infants; its incidence is inversely related to gestational age and birth weight. It occurs in 60–80% of infants less than 28 wk of gestational age, in 15–30% of those between 32 and 36 wk, in about 5% beyond 37 wk, and rarely at term. The risk of developing RDS increases with maternal diabetes, multiple births, cesarean section delivery, precipitous delivery, asphyxia, cold stress, and a history of previously affected infants. The incidence is highest in preterm male or white infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal heroin use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

ETIOLOGY AND PATHOPHYSIOLOGY

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. The failure to attain an adequate FRC and the tendency of affected lungs to become atelectatic correlate with high surface tension and the absence of pulmonary surfactant. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, -B, -C, -D), and cholesterol. With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells. Surfactant is present in high concentrations in fetal lung homogenates by 20 wk of gestation, but it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 wk. Mature levels of pulmonary surfactant are usually present after 35 wk.

Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. Alveolar atelectasis, hyaline membrane formation, and interstitial edema make the lungs less compliant, so greater pressure is required to expand the alveoli and small airways. In affected infants, the lower part of the chest wall is pulled in as the diaphragm descends, and intrathoracic pressure becomes negative, thus limiting the amount of intrathoracic pressure that can be produced; the result is the development of atelectasis. The highly compliant chest wall of preterm infants offers less resistance than that of mature infants to the natural tendency of the lungs to collapse. Thus, at end-expiration, the volume of the thorax and lungs tends to approach residual volume, and atelectasis may develop.

Decreased lung compliance, small tidal volumes, increased physiologic dead space, increased work of breathing, and insufficient alveolar ventilation eventually result in hypercapnia. Pulmonary blood flow is reduced and ischemic injury to the cells producing surfactant and to the vascular bed results in an effusion of proteinaceous material into the alveolar spaces.

PATHOLOGY

The lungs appear deep purplish red and are liver-like in consistency. Microscopically, extensive atelectasis with engorgement of the interalveolar capillaries and lymphatics can be observed. A number of the alveolar ducts, alveoli, and respiratory bronchioles are lined with acidophilic, homogeneous, or granular membranes. The characteristic hyaline membranes are rarely seen in infants dying earlier than 6–8 hr after birth.

CLINICAL MANIFESTATIONS.

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants until rapid, shallow respirations have increased to 60/min or greater. A late onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with a birth weight <1,000 g). Characteristically, tachypnea, prominent (often audible) grunting, intercostal and subcostal retractions, nasal flaring, and duskiess are noted. Cyanosis increases and is often relatively unresponsive to oxygen administration. The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated, blood pressure may fall; fatigue, cyanosis, and pallor increase, and grunting decreases or disappears as the condition worsens. Apnea and irregular respirations occur as infants tire and are ominous signs requiring immediate intervention. Patients may also have a mixed respiratory-metabolic acidosis, edema, ileus, and oliguria. Respiratory failure may occur in infants with rapid progression of the disease. In most cases, the symptoms and signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and the ability to oxygenate the infant at lower inspired oxygen levels or lower ventilator pressures. Death is rare on the 1st day of illness, usually occurs between days 2 and 7, and is associated with alveolar air leaks (interstitial emphysema, pneumothorax), pulmonary hemorrhage, or IVH. Mortality may be delayed weeks or months if BPD develops in mechanically ventilated infants with severe RDS.

DIAGNOSIS.

The clinical course, x-ray of the chest, and blood gas and acid-base values help establish the clinical diagnosis. On x-ray, the lungs may have a characteristic, but not pathognomonic appearance that includes a fine reticular granularity of the parenchyma and air bronchograms, which are often more prominent early in the left lower lobe because of superimposition of the cardiac shadow. The initial roentgenogram is occasionally normal, with the typical pattern developing at 6–12 hr. Considerable variation in films may be seen, depending on the phase of respiration and the use of CPAP or positive end-expiratory pressure (PEEP); this variation often results in poor correlation between roentgenograms and the clinical course. Laboratory findings are initially characterized by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

In the differential diagnosis, early-onset sepsis may be indistinguishable from RDS. In pneumonia manifested at birth, the chest roentgenogram may be identical to that for RDS. Maternal group B streptococcal colonization, organisms on Gram stain of gastric or tracheal aspirates or a buffy coat smear, and/or the presence of marked neutropenia may suggest the diagnosis of early-onset sepsis. Cyanotic heart disease (total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color flow imaging should be performed in infants who fail to respond to surfactant replacement to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance. Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions, and congenital anomalies such as cystic adenomatoid malformation, pulmonary lymphangiectasia, diaphragmatic hernia, and lobar emphysema must be considered, but can generally be differentiated from RDS by roentgenographic evaluation. Transient tachypnea may be distinguished by its short and mild clinical course. Congenital alveolar proteinosis (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants. In atypical cases of RDS, a lung profile (lecithin: sphingomyelin ratio and phosphatidylglycerol level) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency.

PREVENTION

Avoidance of unnecessary or poorly timed cesarean section, appropriate management of high-risk pregnancy and labor, and prediction and possible in utero acceleration of pulmonary immaturity are important preventive strategies. In timing cesarean section or induction of labor, estimation of fetal head circumference by ultrasonography and determination of the lecithin concentration in amniotic fluid by the lecithin: sphingomyelin ratio (particularly useful with phosphatidylglycerol in diabetic pregnancies) decrease the likelihood of delivering a premature infant.

Administration of betamethasone to women 48 hr before the delivery of fetuses between 24 and 34 wk of gestation significantly reduces the incidence, mortality, and morbidity of RDS. Corticosteroid administration is recommended for all women in preterm labor (24–34 wk gestation) who are likely to deliver a fetus within 1 wk. Repeated weekly doses of betamethasone until 32 wk may reduce neonatal morbidities and the duration of mechanical ventilation. Prenatal glucocorticoid therapy decreases the severity of RDS and reduces the incidence of other complications of prematurity, such as IVH, patent ductus arteriosus (PDA), pneumothorax, and necrotizing enterocolitis, without adversely affecting postnatal growth, lung mechanics or development, or the incidence of infection. Prenatal glucocorticoids may act synergistically with postnatal exogenous surfactant therapy. Prenatal dexamethasone may be associated with a higher incidence of periventricular leukomalacia than betamethasone. The relative risk of RDS, IVH and death is higher with antenatal dexamethasone treatment when compared with betamethasone.

TREATMENT

The basic defect requiring treatment is inadequate pulmonary exchange of oxygen and carbon dioxide; metabolic acidosis and circulatory insufficiency are secondary manifestations. Early supportive care of LBW infants, especially in the treatment of acidosis, hypoxia, hypotension and hypothermia may lessen the severity of RDS. Treatment of these infants is best carried out in a specially staffed and equipped hospital unit, the neonatal intensive care unit (NICU).

Warm humidified oxygen to keep arterial levels between 50 and 70 mm Hg (85–95% saturation) and minimizing the risk of oxygen toxicity. If the Pao₂ cannot be maintained above 50 mm Hg at inspired oxygen concentrations of 60% or greater, applying CPAP by nasal prongs is indicated. Another approach is to intubate the VLBW infant, administer intratracheal surfactant, and then extubate to CPAP.

Reasonable indications for mechanical ventilation use are-

- (1) arterial blood pH < 7.20, (2) arterial blood Pco₂ of 60 mm Hg or higher,
- (3) arterial blood Po₂ of 50 mm Hg or less at oxygen concentrations of 70–100% and CPAP of 6–10 cm H₂O, or (4) persistent apnea.

Multidose endotracheal instillation of exogenous surfactant to VLBW infants requiring 30% oxygen and mechanical ventilation improves survival and reduces the incidence of pulmonary air leaks, but it has not reduced the incidence of BPD. A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. Exosurf is a synthetic surfactant. Natural surfactants include Survanta (bovine), Infasurf (calf), and Curosurf (porcine). Although both synthetic and natural surfactants are effective in the treatment and prevention of RDS, natural surfactants appear to be superior, perhaps because of their surfactant-associated protein

content. Rescue treatment is initiated as soon as possible in the 1st 24 hr of life. Repeated dosing is given via the endotracheal tube every 6–12 hr for a total of 2 to 4 doses, depending on the preparation.

Inhaled nitric oxide (iNO) decreases the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure. Low-dose iNO may decrease the incidence of BPD in critically ill premature infants. A reduction in the rate of death or BPD in infants <1,000 g treated with iNO was observed in one study. iNO treatment of RDS may also be associated with improved neurodevelopmental outcome. Metabolic acidosis in RDS may be a result of perinatal asphyxia and hypotension and is often encountered when an infant has required resuscitation.

Alkali (sodium bicarbonate) therapy may result in skin slough from infiltration, increased serum osmolarity, hypernatremia, hypocalcemia, hypokalemia, and liver injury when concentrated solutions are administered rapidly through an umbilical vein catheter wedged in the liver. Because of the difficulty of distinguishing group B streptococcal or other bacterial infections from RDS, empirical antibiotic therapy is indicated.

COMPLICATIONS OF RDS AND INTENSIVE CARE.

The most serious complications of tracheal intubation are asphyxia from obstruction of the tube, cardiac arrest during intubation or suctioning, and the subsequent development of subglottic stenosis.

Measures to reduce the incidence of these complications include skillful intubation. Risks associated with umbilical arterial/venous catheterization include vascular embolization, thrombosis, spasm, and vascular perforation; ischemic or chemical necrosis of abdominal viscera; infection; accidental hemorrhage; and impaired circulation to a leg with subsequent gangrene.

Manifestations of PDA may include-

(1) Apnea for unexplained reasons in an infant recovering from RDS. (2) A hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a continuous or systolic murmur. (3) Carbon dioxide retention. (4) Increasing oxygen dependence. (5) X-ray evidence of cardiomegaly and increased pulmonary vascular markings. (6) Hepatomegaly.

The diagnosis is confirmed by echocardiographic . Interventions include fluid restriction, the use of diuretics, the use of cyclo-oxygenase inhibitors, and surgical closure. Indomethacin is the drug of choice for medical closure of the PDA. Bronchopulmonary dysplasia (BPD) is a result of lung injury in infants at risk for classic BPD usually have severe respiratory distress requiring prolonged periods of mechanical ventilation and oxygen therapy. Treatment of BPD includes nutritional support, fluid restriction, drug therapy, maintenance of adequate oxygenation, and prompt treatment of infection. Growth must be monitored because recovery is dependent on the growth of lung tissue.

PROGNOSIS

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal steroids, postnatal surfactant use, improved modes of ventilation, and developmentally appropriate care have resulted in low mortality from RDS (from 40% to \approx 10%). Mortality increases with decreasing gestational age.