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Core Concepts: Respiratory Distress Syndrome

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Drs Warren and
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Objectives After completing this article, readers should be able to:

1. Define respiratory distress syndrome (RDS).
2. Discuss the epidemiology, pathophysiology, and diagnosis of RDS.
3. Create a differential diagnosis for respiratory distress in the neonate.
4. Describe the proven treatments for RDS, with particular attention to antenatal steroids and surfactant replacement therapy (SRT), their benefits and possible complications.
5. Discuss ventilation strategies that can be used in the infant who has RDS.
6. Describe long-term complications of RDS and its treatments.

Abstract

Respiratory distress syndrome (RDS) is seen primarily in the preterm neonate and is due mostly to pulmonary surfactant deficiency. Lung atelectasis leads to ventilation-perfusion mismatching, hypoxia, and eventual respiratory failure in the untreated infant who has RDS. RDS is diagnosed by physical findings consistent with respiratory distress and characteristic radiographic findings. Treatment of RDS begins antenatally with the administration of maternal steroids to women at risk of preterm delivery between 24 and 34 weeks' gestation. The use of repeat doses of antenatal steroids is under investigation but is currently not recommended outside of randomized, controlled trials. SRT has been approved for use since 1990 and has been successful in decreasing rates of RDS. Natural surfactant is currently recommended for use, but synthetic surfactant that contains proteins to mimic surfactant proteins is being investigated. In general, prophylactic use of surfactant is recommended over rescue treatment in infants at high risk for developing RDS, but the determination of which infants are at high risk for developing RDS remains a clinical one. The push toward use of less invasive ventilation strategies in the treatment of RDS has led to several trials of nasal continuous positive airway pressure (nCPAP). Results of the SUPPORT trial are pending, but the COIN trial has concluded that nCPAP use in infants who have RDS is not detrimental. Inhaled nitric oxide for RDS still requires investigation on safety and efficacy. Several other treatments have been studied, but as of yet, only inositol administration shows promise in the treatment of RDS. Several complications of the recommended treatments for RDS have been identified, but the benefits far outweigh the risks. Finally, there remains a need for long-term follow-up studies on preterm infants treated for RDS to assess neurodevelopmental outcomes.

Definition

RDS, formerly known as hyaline membrane disease, occurs in incompletely developed lungs and is, therefore, a disease of prematurity. Immature lungs are functionally deficient in mature surfactant. (1) The absence of surfactant in the liquid film lining of alveoli causes an increase in surface tension and alveolar collapse. (2) If not treated, such atelectasis causes an increased work of breathing, intrapulmonary shunting, ventilation-perfusion mismatch, hypoxia, and eventual respiratory failure. (1)

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Epidemiology

RDS is seen almost exclusively in preterm infants, before the lungs begin to manufacture adequate amounts of surfactant. (2) In fact, the risk of RDS decreases with increasing gestational age: 60% of babies born at fewer than 28 weeks' gestation, 30% of babies born between 28 and 34 weeks' gestation, and fewer than 5% of babies born after 34 weeks' gestation develop RDS. (3) Other factors that increase the risk of RDS include male sex, maternal gestational diabetes, perinatal asphyxia, hypothermia, and multiple gestations. (4) Antenatal steroids and prolonged rupture of membranes decrease the risk of RDS. (5) With the advent of therapies for RDS, including antenatal steroids and SRT, mortality from RDS has decreased from nearly 100% to less than 10% in recent years. (6)

Differential Diagnosis

The differential diagnosis of respiratory distress in the newborn encompasses upper respiratory obstruction, pulmonary disease, cardiac disease, thoracic causes, metabolic disorders, diaphragmatic causes, neuromuscular diseases, infectious causes, hemolytic/vascular causes, and miscellaneous causes (Table 1). (7)(8)

Pathophysiology

Normal Lung Development

The period of viability begins at around 23 weeks' gestation, when the fetal lung begins to transition from the canalicular to the saccular stage of development (Table 2). (9) During the saccular stage, peripheral airways

enlarge and distal airways begin to dilate while their walls begin to thin. (10) Type II pneumocytes, the cells responsible for surfactant production, are present and maturing. (10) Although gas exchange is possible during this stage, total surface area for gas exchange is low and diffusion distance for gas exchange is high in relation to body weight and metabolic rate. (9) Secondary septation, or alveolarization, begins at about 32 weeks' gestation. (9) During this phase, alveoli form and mature and alveolar walls thin. (10) All cell types proliferate during this phase, including type II pneumocytes. (10) The overall result is a maturing lung with a larger surface area and a minimal diffusion distance for gas exchange. (10)

Surfactant Composition and Life Cycle

Surfactant is a mixture of phospholipids and proteins. (2) The most abundant surface-active phospholipid in mature lungs is phosphatidylcholine. (11) Phosphatidylcholine forms a monolayer on the liquid film lining of the alveolus, lowering the surface tension of that film. (2) In addition to phospholipids, surfactant contains four major proteins: surfactant proteins (SPs) A, B, C, and D (Table 3). (11) SP-A helps to regulate surfactant secretion and uptake; SP-B and SP-C facilitate adsorption and spreading of phospholipids on the liquid film lining of the alveoli. (2) SP-D may play a role in surfactant reuptake and recycling. (5)

Pulmonary surfactant is manufactured in the Golgi apparatus and stored in lamellar bodies of type II pneumocytes. (5) Once secreted by the lamellar bodies into the extracellular space, surfactant is organized into tubular myelin, adsorbed into the air-water interface, and formed into a lipid monolayer. (5)(6) The surface-active properties of the lipid monolayer decrease the surface tension of the air-water interface and prevent alveolar collapse. (6) The majority of surfactant constituents are believed to be recycled, either through reuptake by type II pneumocytes or by alveolar macrophages. (9)

RDS

An infant born before the alveolarization stage of lung development has underdevelopment of alveolar sacs and difficulty with oxygenation and ventilation. (9) Similarly, an infant born before this stage of lung development experiences a delay in production and secretion of functional surfactant. (9) Such surfactant deficiency is the major reason for poor lung function in the preterm neonate (Table 4). (2)

Although the preterm neonate does produce a small amount of surfactant, this surfactant contains low amounts of phospholipids and SPs. (9) It is estimated

Abbreviations

AT:	antithrombin
BPD:	bronchopulmonary dysplasia
CLD:	chronic lung disease
FRC:	functional residual capacity
GBS:	group B <i>Streptococcus</i>
iNO:	inhaled nitric oxide
IVH:	intraventricular hemorrhage
nCPAP:	nasal continuous positive airway pressure
NIH:	National Institutes of Health
NIMV:	nasal intermittent mandatory ventilation
PIE:	pulmonary interstitial emphysema
PVL:	periventricular leukomalacia
RDS:	respiratory distress syndrome
SP:	surfactant protein
SRT:	surfactant replacement therapy

Table 1. Differential Diagnosis of Respiratory Distress in the Newborn

Upper Airway Obstruction

Choanal atresia, nasal stenosis, Pierre Robin sequence, laryngeal stenosis or atresia, hemangioma, vocal cord paralysis, vascular rings, tracheobronchial stenosis, masses, cleft palate, nasal stuffiness

Pulmonary Diseases

Respiratory distress syndrome, retained fetal lung liquid syndrome (transient tachypnea of the newborn), aspiration (including meconium aspiration syndrome), pneumonia, pneumothorax, pneumomediastinum, primary pulmonary hypertension, tracheoesophageal fistula, pulmonary hemorrhage, pulmonary hypoplasia, pulmonary agenesis, cystic disease, pleural effusion, chylothorax, neoplasm, bronchopulmonary sequestration, pulmonary arteriovenous malformation, pulmonary interstitial emphysema, pulmonary edema, congenital alveolar proteinosis, congenital lobar emphysema

Cardiac Diseases

Cyanotic congenital heart disease, acyanotic congenital heart disease, arrhythmia, increased intravascular volume, high output failure, pneumopericardium, cardiomyopathy

Thoracic Causes

Chest wall deformity, mass

Metabolic Disorders

Hypoglycemia, infant of a diabetic mother, inborn errors of metabolism

Diaphragmatic Causes

Hernia, paralysis

Neuromuscular Diseases

Central nervous system damage (birth trauma, hemorrhage), medication (maternal sedation, narcotic withdrawal), muscular disease (myasthenia gravis), intraventricular hemorrhage, meningitis, hypoxic-ischemic encephalopathy, seizure disorder, obstructed hydrocephalus, infantile botulism, spinal cord injury

Infectious Causes

Sepsis, pneumonia (especially group B *Streptococcus*)

Hemolytic/vascular Causes

Anemia, polycythemia, abnormal hemoglobin

Miscellaneous Causes

Asphyxia, acidosis, hypo/hyperthermia, hypo/hypernatremia

that infants who have RDS have surfactant pools of less than 10 mg/kg compared with pools of up to 100 mg/kg in term infants. Such surfactant deficiency necessitates increased work of breathing to distend alveoli, which the preterm neonate may not be able to provide. (2) Diffuse atelectasis ensues and leads to an overall decrease in functional residual capacity (FRC) of the lungs. (2) If an infant is allowed to breathe from an

inadequate FRC, lung injury can occur. (9) Lung injury leads to protein exudation and edema, which can inactivate surfactant further. The acidosis and hypoxia that results from atelectasis and lung injury further interferes with surfactant production. The combination of these events leads to respiratory failure.

Diagnosis

Clinical Evaluation

RDS presents at the time of or soon after birth, and symptoms worsen over time. (2) Clinical symptoms of RDS are the same as those of any other respiratory distress: tachypnea, nasal flaring, chest wall retractions, expiratory grunting, and central cyanosis. (2) In the extremely preterm infant, the only clinical symptom of RDS may be apnea. (2) It is important to remember that some infants who have RDS exhibit all of these symptoms, and others may show none.

An accurate history is important in diagnosing RDS. As stated, RDS is more prevalent in earlier gestational ages, so an accurate estimation of gestational age is necessary. Other historical factors must be discerned, such as antenatal steroid therapy; maternal history of gestational diabetes; course of labor, including prolonged rupture of membranes, maternal fever, group B *Streptococcus* (GBS) status and antibiotic therapy; method of delivery; and need for resuscitation.

Diagnostic Studies

Along with the history and physical examination, a chest radiograph is needed for the diagnosis of RDS. The typical chest radiograph shows diffuse atelectasis and the classic “ground glass” appearance of the lung fields (Figure). (2) Air bronchograms, which are air-filled bronchi superimposed on the relatively airless parenchyma of the lung tissue, also are seen commonly on chest radiograph. (2) Importantly, the appearance of GBS pneumonia on

Table 2. Normal Lung Development (10)

Phase	Embryonic	Pseudoglandular	Canalicular	Saccular	Alveolar
Gestation (weeks)	~0 to 7	~7 to 17	~17 to 27	~28 to 36	~36+
Structures	Trachea and bronchi	Conducting airways and terminal bronchioles	Respiratory bronchioles, alveolar ducts, primitive alveoli	Enlarged peripheral airways, thinned alveolar walls	Definitive alveoli
Type II Pneumocytes	Absent	Immature; undifferentiated	Immature; differentiated	Developing laminar bodies	Mature

chest radiograph can be identical to that of RDS. (12) Empiric antibiotics to address GBS infection should be started until such disease is ruled out. Arterial blood gas measurements show hypercarbia and hypoxia and eventually, in the unsupported infant, metabolic acidosis. (2) In all, a preterm infant must have clinical signs of respiratory distress and a classic chest radiograph to be diagnosed with RDS. (2)

Management

Antenatal Steroids

Antenatal steroid administration to women at high risk of preterm delivery prior to 34 weeks' gestation has been standard of care since the 1994 National Institutes of Health (NIH) Consensus Conference. (13) A Cochrane review by Roberts and Dalziel from 2006 confirmed the benefits of antenatal steroids, which include decreases in neonatal death, intraventricular hemorrhage (IVH), and RDS. (1) Antenatal steroids are believed to decrease the incidence of RDS by accelerating maturation of the fetal lung. (13)

Early studies on the use of antenatal steroids did not include data on babies who were delivered before

28 weeks' gestation, so there was a question of whether antenatal steroids would be beneficial in this age group. The Roberts and Dalziel review shows that when steroids are administered initially at 26 weeks' gestation, there is a decreased incidence of RDS that is not seen if steroids are administered before 26 weeks' gestation. (1) However, the incidence of IVH still may be reduced if steroids are administered at fewer than 26 weeks' gestation. (1) Therefore, because of the apparent benefit to preterm infants in terms of decreased IVH, antenatal corticosteroid administration is recommended for preterm infants starting at 24 weeks' gestation. (13)

Both betamethasone and dexamethasone have been studied and found to be more effective than placebo, but these steroids have not been examined head-to-head. (13) The Roberts and Dalziel review suggests that betamethasone may cause a larger reduction in RDS than dexamethasone. (1) Baud and colleagues (14) found that antenatal exposure to betamethasone, but not dexamethasone, is associated with a decreased risk of periventricular leukomalacia (PVL) in preterm infants, but there is no difference in the incidence of cerebral palsy. (1) With this limited evidence, two doses of betamethasone administered 24 hours apart is currently the recommended steroid for antenatal use. (13)

Antenatal steroid administration has been shown to be beneficial if provided fewer than 24 hours before

Table 3. Surfactant Proteins and Their Functions (5)

Surfactant Proteins	Functions
SP-A	Part of the host innate immune defense Facilitates the formation of tubular myelin Regulates surfactant secretion and uptake
SP-B	Promotes adsorption and spreading of pulmonary surfactant
SP-C	Promotes adsorption and spreading of pulmonary surfactant
SP-D	Part of the host innate immune defense May play a role in pulmonary surfactant reuptake and recycling

Table 4. Results of Surfactant Deficiency (2)

1. Decreased lung compliance
2. Unstable alveoli
3. Decreased functional residual capacity
4. Hypoxia (from shunting of blood through atelectatic portions of the lung)
5. Increased work of breathing
6. Lung edema (exudation of fluid and serum proteins)



Figure. Classic chest radiograph in an infant who has RDS.

delivery. Therefore, steroid administration is recommended before delivery of preterm infants 24 to 34 weeks' gestation unless delivery is imminent. (13) Furthermore, a reduction in RDS has been seen in infants born up to 7 days after the first dose of antenatal steroids was administered. (1) No benefit is seen in infants who receive the first dose of steroids more than 7 days before birth. (1)

Because antenatal steroids seem to be of benefit only when administered from just before birth to 7 days before delivery, the utility of repeated antenatal steroid dosing has been studied. The latest Cochrane review on the subject, conducted by Crowther and Harding in 2007, suggests that repeat doses of prenatal steroids do reduce the incidence and severity of neonatal lung disease in the first few postnatal weeks. (15) They recommend repeat doses of corticosteroids in women at risk for preterm birth when the first course of steroids was administered more than 7 days previously because of the short-term benefits to the fetal lungs. They do, however, warn about the possibility of decreased birthweight and head circumference at birth, which has been reported. For example, repeat antenatal steroid courses in fetal sheep result in increased lung maturation as well as increased growth restriction. (13) Guinn and colleagues

(16) showed that the composite neonatal morbidity, including severe RDS, bronchopulmonary dysplasia (BPD), severe IVH, PVL, sepsis, necrotizing enterocolitis, or perinatal death, was not reduced by using weekly courses as compared with one course of antenatal steroids. Because the true risk-to-benefit ratio of using repeat doses of antenatal steroids is not known, the 1994 and 2000 NIH Consensus Conference recommends the use of repetitive courses of steroids only in the context of randomized, controlled trials (Table 5). (13)

Surfactant

SRT was approved for use by the United States Food and Drug Administration in 1990. (5) Immediate improvement in oxygenation, along with improved aeration on chest radiograph within 1 hour, is seen after administration of SRT. (5)(17) SRT reduces the incidence of RDS, death, pneumothorax, pulmonary interstitial emphysema (PIE), and IVH in preterm infants. (17) Although most available evidence suggests that SRT increases survival rates without increasing the risk of disability, the risk of long-term disability is unknown due to few reported

Table 5. Summary of 1994 and 2000 National Institutes of Health Consensus Conference Antenatal Steroid Recommendations

1. The benefits of prenatal corticosteroids outweigh any risks that have been identified. The benefits include decreased death and decreased incidence of respiratory distress syndrome and intraventricular hemorrhage.
2. All fetuses at 24 to 34 weeks' gestation are candidates for corticosteroid therapy.
3. Prenatal corticosteroid therapy should be used without consideration of fetal sex, race, or the availability of surfactant treatments for respiratory distress syndrome.
4. Prenatal corticosteroids should be administered if tocolytics are used.
5. Because of probable benefit for treatment to delivery intervals of less than 24 hours, prenatal corticosteroids are indicated unless delivery is imminent.
6. Repeated courses of corticosteroids may not be safe and should not be administered outside of clinical trials.

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follow-up studies on the preterm infants who have received surfactant. (17)

Surfactant is administered directly into the lungs via an endotracheal tube. (5) Other methods of surfactant administration, including aerosolization, nebulization, and instillation via bronchoalveolar lavage, have been found to be ineffective. (5) Surfactant administration via laryngeal mask airway is being studied. (5) Surfactant can be administered as either two or four fractional doses in either two or four different body positions; clinical evidence is not sufficient to recommend an optimal number of fractional doses. (17) Surfactant can be administered as either a bolus or an infusion into the endotracheal tube; again, data in humans are insufficient to recommend an optimal method of surfactant administration. (17) Interestingly, data examining the distribution of surfactant in mechanically ventilated rabbits showed that bolus instillation resulted in reasonably homogenous pulmonary surfactant distribution, while tracheal infusion resulted in extremely uneven pulmonary distribution. (18)

Natural and synthetic surfactant preparations exist, and both are effective in the treatment and prevention of RDS. (19) Natural surfactants are derived from animal lungs (bovine or porcine) and contain phospholipids with SP-B and SP-C; first-generation synthetic surfactants contain only phospholipids without proteins. (19) A Cochrane meta-analysis by Soll and Blanco conducted in 2001 comparing natural surfactant to first-generation synthetic surfactant confirmed that natural surfactant more effectively reduces the risk of pneumothorax and lowers mortality rates in infants treated for RDS. (20) There is also a marginal decrease in the risk of BPD when using natural surfactant. Although natural surfactants appear to be associated with higher rates of IVH, grade 3 and 4 IVH rates are not increased. The conclusion of this meta-analysis is that natural surfactants are the more desirable choice over the first-generation synthetic surfactants, which is likely due to the inclusion of the SPs in the natural surfactant. (20)

Synthetic surfactants containing peptides that mimic SPs recently have been developed and tested. (21) In a meta-analysis of two studies comparing protein-containing synthetic surfactant to natural surfactant, no statistically significant differences were found between the two groups in terms of death or chronic lung disease (CLD), and clinical outcomes were generally similar. (21) Further studies comparing these two groups are needed.

The use of prophylactic versus selective administration of surfactant has been studied thoroughly. Prophylactic SRT involves intubation and surfactant administra-

tion in preterm infants at high risk for RDS and usually occurs after the initial resuscitation and within 10 to 30 minutes of birth. (17) Prophylactic SRT has the advantage of establishing a normal surfactant pool before damage due to a low FRC, and an increased work of breathing can occur. (5) Its major disadvantage is the possibility that an infant who would not have developed RDS may be intubated and treated with surfactant. (5) Selective, or rescue, SRT is the administration of surfactant to preterm infants who already have developed RDS. (17) The two types of selective SRT are early and late. (17) Early selective SRT is administered within 1 to 2 hours of birth; late selective SRT occurs 2 or more hours after birth. The advantage of selective SRT is the avoidance of overtreatment, but in those infants who develop RDS, the delay in treatment allows lung inflammation and damage to occur. (5)

In the Cochrane review by Soll and Morley in 2001, the use of prophylactic surfactant in infants at high risk of developing RDS was compared with selective surfactant treatment at the time of respiratory failure. (22) Prophylactic surfactant treatment was associated with a significant reduction in the risk of pneumothorax, PIE, mortality, and BPD or death. (22) A secondary analysis of infants of fewer than 30 weeks' gestation found a significant decrease in the risk of mortality and the risk of BPD or death. The conclusion of this study is that prophylactic surfactant is beneficial in preterm infants believed to be at high risk for developing RDS, but the best method of determining if an infant is at high risk for developing RDS remains unclear. (22)

Because the incidence of RDS decreases with increasing gestational age, it becomes likely that prophylactic treatment with surfactant once gestational ages approach 28 to 30 weeks results in a good percentage of overtreatment. (5) In these cases, it may make more sense to treat selectively with surfactant. The most recent Cochrane review examining early versus late selective surfactant administration found that early selective SRT decreased neonatal mortality, pneumothoraces, PIE, and the incidence of CLD and death at 36 weeks' postmenstrual age when compared with late selective SRT. (5)

Finally, in 1999, a Cochrane review compared multiple versus single doses of natural surfactant for the treatment of RDS. (23) The reason for this comparison was the observation that some infants seemed to relapse after initial surfactant treatment. In this meta-analysis, a more sustained response in the treatment of RDS was seen in the group of infants allowed to have multiple doses of surfactant. (23) A decreased risk of pneumotho-

rax and a trend toward a decreased risk of mortality also was reported.

Overall, survival without BPD has increased since SRT began, although the incidence of BPD in very low-birthweight infants is unchanged. (17) The risk of respiratory problems later in infancy or childhood (including asthma and infection) remains high for preterm infants who were treated with surfactant and mechanical ventilation. (17) Long-term studies are needed to assess the respiratory function of children who received surfactant as preterm infants. (17)

Antenatal Steroids and Surfactant

No randomized, controlled trials have been conducted to address whether antenatal steroids reduce the need for prophylactic or rescue SRT in preterm infants. (17) On subgroup analyses of observational studies and clinical trials, infants born before 32 weeks' gestation who received both antenatal steroids and SRT had significant reductions in mortality, severity of respiratory distress, and frequency of air leaks compared with infants who received neither treatment, only antenatal steroids, or only SRT. (17) Infants born before 27 weeks' gestation did not have a lower incidence of RDS, but the severity of RDS may have been decreased. Therefore, it is generally accepted that the effects of antenatal steroids and SRT are additive, and it is not expected that trials will be conducted to verify this.

Ventilatory Management

Several methods can be used to ventilate the preterm neonate at risk for RDS. Surfactant administration followed by conventional ventilation has historically been the management of choice, but concerns that both positive pressure ventilation via the endotracheal tube and the duration of mechanical ventilation have direct effects on the incidence of BPD have prompted investigators to search for less harsh ventilatory strategies. (24)(25) Because most preterm infants who have RDS require ventilatory support and BPD is a major morbidity of many forms of ventilatory support, the hope is to find a noninvasive method of ventilation for RDS that is both safe and effective.

The initial belief was that more complex ventilation strategies, such as high-frequency oscillatory ventilation, might decrease the risk of developing BPD. However, when optimal lung volume strategies are used, there is no difference between conventional ventilators and high-frequency ventilators in terms of pulmonary and nonpulmonary outcomes. (24)(25) A Cochrane review on this

subject from 2007 confirmed the lack of clear evidence for elective use of high-frequency ventilation over conventional ventilation because no difference was documented in mortality between the two modes of ventilation at 30 days or at term-equivalent age. (26) Patient-triggered ventilation is a form of conventional ventilation that includes synchronized intermittent mandatory ventilation, assist control, and pressure support. (24)(25) Studies have shown that patient-triggered ventilation has benefits over conventional ventilation and high-frequency ventilation in terms of a decreased duration of mechanical ventilation and decreased number of days on oxygen. (24)(25) However, there was no significant difference in terms of a decrease in lung injury between the three ventilation strategies.

The noninvasive ventilation strategy of nCPAP is believed to work by improving oxygenation without increasing PaCO₂ through the stabilization and recruitment of collapsed alveoli. (27) The idea is that nCPAP will help to achieve the adequate FRC that is necessary to avoid the development of RDS because increased FRC means increased alveolar surface area and less intrapulmonary shunt. (27) The avoidance of endotracheal intubation saves the infant from the barotrauma and volutrauma seen with the use of mechanical ventilators. A Cochrane Review from 2002 states that although a higher rate of pneumothorax was seen, there was an overall reduction in respiratory failure and mortality in preterm infants who had RDS and were treated with nCPAP. (28) Large randomized, controlled trials to evaluate this possibility are underway.

The COIN trial (Continuous Positive Airway Pressure or Intubation at Birth) is a recently published randomized trial addressing whether the use of nCPAP shortly after birth would decrease the rates of death and BPD (defined as the need for oxygen at 36 weeks gestational age). (29) A total of 610 infants from gestational ages 25 to 28 and 6/7 weeks were randomized at 5 minutes after birth to receive either nCPAP or intubation and mechanical ventilation. Outcomes between the two groups were assessed at 28 days, 36 weeks gestational age, and before discharge. There was a significantly lower risk of death or need for oxygen at 28 days in the nCPAP-treated infants, but early nCPAP did not significantly decrease the rates of death or BPD compared with intubation and ventilation at 36 weeks gestational age. Infants in the nCPAP group required fewer overall days of ventilation, but also had a significant increase in pneumothoraces compared with mechanically ventilated infants. The overall conclusion of the study was that early

nCPAP was not detrimental to preterm infants whose gestational ages were between 25 and 28 and 6/7 weeks. (29)

The SUPPORT trial (Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth-weight Infants) is currently ongoing. This trial is randomizing infants of gestational ages between 24 weeks and 27 and 6/7 weeks to either a treatment group of CPAP and permissive ventilation management or a control group of prophylactic/early surfactant and conventional ventilator management as well as either a low (85% to 89%) or high (91% to 95%) SpO₂ group. Results of this study are pending. (30)

Finally, nasal intermittent mandatory ventilation (NIMV) has been studied in the treatment of RDS. The rationale for NIMV use is that the administration of “sighs” to the neonate can help to open microatelectasis and recruit more alveoli. (31) Kugelman and associates (31) showed that NIMV was more successful than nCPAP in the initial treatment of RDS among infants younger than 35 weeks’ gestation by reducing the rate of endotracheal intubation and the incidence of BPD. (31) As with other studies, failure of nasal respiratory support was associated with lower birthweight. Further study is needed, but NIMV may be a promising non-invasive method of ventilation for preterm infants at risk for RDS.

Ventilatory Management and Surfactant

Surfactant is a proven treatment for RDS that must be administered via endotracheal tube. As ventilation strategies become more sophisticated and less invasive, the use of surfactant may become more complicated. The push toward less invasive ventilation strategies does not allow an opportunity for surfactant administration. To allow for use of surfactant, many centers have started to intubate, administer surfactant, and extubate to minimally invasive respiratory support (“in-and-out surf”). A recent Cochrane Review compared early surfactant administration with brief ventilation to selective surfactant with continued mechanical ventilation in preterm infants who had or were at risk for RDS. (32) The use of surfactant followed by early extubation to nCPAP was more effective than selective intubation and surfactant administration followed by mechanical ventilation in preventing the need for mechanical ventilation as well as decreasing the incidence of BPD and pneumothorax. (32) No investigators currently are examining the use of early and continuous nCPAP versus surfactant administration followed by early extubation and nCPAP.

Inhaled Nitric Oxide (iNO)

NO is a vascular endothelial relaxing factor that successfully causes local smooth muscle cell relaxation in the pulmonary circulation when delivered by inhalation. (33) iNO has been used as a treatment in illnesses in which pulmonary vasodilation would be of benefit. Pulmonary hypertension is recognized as a complicating factor that may contribute to RDS. (33) The ability of iNO to dilate the blood vessels in the pulmonary vasculature, reduce pulmonary hypertension, and improve ventilation-perfusion matching (a known problem in RDS) has led to clinical trials on the use of iNO in the preterm infant who has RDS. (33) Of note, one major concern for the use of iNO in preterm infants is the adverse effect of bleeding complications.

In the Cochrane Review conducted by Barrington and Finer in 2007, iNO possibly improved outcome in mildly ill infants, with a possible decrease in ICH. (34) However, when administered to very ill preterm infants, iNO did not improve outcome and may have contributed to an increase in ICH. (34) Overall, the benefit of iNO in the preterm infant is largely unknown, and further randomized, controlled trials with subsequent meta-analyses are needed to answer this question. (33)

Other

Several other therapies have been studied as possible treatments for RDS. The following therapies have been reviewed in meta-analyses and published in the Cochrane Database of Systematic Reviews.

DIURETICS. RDS may be complicated by lung edema, so studies have been performed to determine if administration of diuretics may improve the course of RDS. A Cochrane Review by Brion and Soll in 2007 (35) analyzed seven studies with the aim of assessing risks and benefits of diuretic use in preterm infants who had RDS. Six of these studies used furosemide and were conducted before the era of prenatal steroids and surfactant. Although a transient furosemide-induced improvement in pulmonary function was seen, this benefit did not outweigh the risk for patent ductus arteriosus and hemodynamic instability. There were no long-term benefits. The other study assessed theophylline use and found no long-term benefits. Overall, the reviewers of these studies did not find data to support the routine administration of furosemide or theophylline in preterm infants who had RDS. (35)

ANTITHROMBIN (AT). AT is produced by the liver and is important in both blood clotting and clot lysis. Infants

who have RDS, as well as infants who have other critical illnesses, have low serum AT concentrations. It was hypothesized that increased thrombin formation due to low AT concentrations might contribute to the pathophysiology of RDS and that administration of AT may improve the clinical course of affected infants. A review by Bassler and associates (36) found a trend toward increased mortality as well as a significantly prolonged duration of mechanical ventilation and oxygen therapy in the AT-treated group. Therefore, due to the lack of benefit, as well as the potential harm, AT is not a recommended treatment for infants who have RDS.

DIGOXIN. It has been suggested that pulmonary edema due to congestive heart failure may contribute to RDS in the neonate. Based on this suggestion, digoxin has been studied as a potential treatment in RDS. Two randomized, controlled trials were analyzed by Soll, (37) who found that digoxin did not result in improved RDS symptoms. Therefore, digoxin is not recommended for use in infants solely affected with RDS.

INOSITOL. Inositol is a nutrient required by cells for growth and survival that also has been found to promote maturation of several components of surfactant. A 2003 review by Howlett and Ohlsson (38) includes three randomized, controlled trials of the use of inositol in preterm infants who had RDS. A significant reduction in death or BPD, stage 4 retinopathy of prematurity, and grade 3 or 4 IVH was seen in the inositol-treated group. No significant increase in adverse effects was reported. Due to the relatively small number of infants in these reviewed trials, multicenter randomized, controlled trials are recommended. However, these early results on the use of inositol in preterm infants with RDS are promising.

POSTNATAL THYROID HORMONE. Animal research has shown that antenatal administration of thyroid hormone stimulates surfactant production and reduces the incidence and severity of RDS. A review by Osborn and Hunt (39) examined trials that used postnatal thyroid hormone in preterm infants who had RDS. The conclusion was that administration of thyroid hormone therapy within the first hours after birth had no significant effect on the severity of RDS, morbidity, or mortality in such preterm infants and, therefore, is not recommended.

Complications and Treatment of RDS

A major pulmonary complication of RDS is the development of BPD, which is generally defined as the need for

oxygen supplementation at 36 weeks' corrected gestational age. (11) Importantly, BPD is not caused by RDS; rather, it can be the result of the many treatments of RDS. (40) The "new BPD," a term coined by Jobe in 1999, describes a syndrome that results from processes that interfere with lung development, not a syndrome resulting only from injury. (40) These processes can include chorioamnionitis, oxygen administration, high tidal volumes, mechanical ventilation, postnatal sepsis, and postnatal corticosteroids. Accordingly, it is possible to develop BPD without having RDS, but BPD absolutely can occur in preterm infants who developed and were treated for RDS. (40) Other complications of RDS in the preterm infant include IVH, patent ductus arteriosus, sepsis, and pulmonary hemorrhage, which likely result from a combination of prematurity, RDS, and its treatments.

Complications from the treatments for RDS are inevitable, but based on risk-to-benefit ratios of the treatments, the complications are mostly tolerable. Antenatal steroids do not have true short-term complications when examined in meta-analyses; there has been no associated increase in maternal death, maternal infection, fetal death, neonatal CLD, or neonatal birthweight. (1) Concerns of decreased birthweight (15) as well as trends toward increased incidence of IVH and long-term adverse behaviors have been voiced with the use of multiple repeat doses of antenatal steroids, but never consistently proven. (16) Interestingly, in a 30-year follow-up of infants who received antenatal corticosteroids, no change in adult size or blood lipid or cortisol concentrations was documented, but there was a slight increase in the incidence of insulin resistance. (13) These results may have implications for the hypothesis of the fetal origins of adult disease. (1)

Mild complications of surfactant administration may include transient oxygen desaturation, apnea, and bradycardia, but such complications typically improve rapidly. (5) More serious complications include endotracheal tube blockage and pulmonary hemorrhage. (5) After administration, surfactant may distribute unevenly to only one lung or certain lobes. A second dose generally follows the same course as the first, which can lead to continued atelectasis of certain areas of the lungs. (9) As mentioned, natural surfactant administration causes an increase in grade 1 and 2 IVH compared with synthetic surfactant. (20) Finally, after surfactant administration, the clinical signs of a PDA may develop earlier in the clinical course. (17)

Complications of mechanical ventilation are not specific to infants being treated for RDS. Air leak syn-

dromes, including PIE and pneumothorax, are more common when the poorly compliant lungs in RDS are mechanically ventilated. (2) Pneumothorax is also associated with the use of nCPAP. (29)

Long-term Prognosis

Survival of infants who have RDS has improved greatly with the use of antenatal steroids and SRT. Preliminary data in infants treated with antenatal steroids suggest the possibility of less neurodevelopmental delay. (1) Overall, however, information regarding neurodevelopmental outcomes in the preterm infants treated for RDS is lacking, and long-term follow-up studies are needed.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the pathophysiology and risk factors for RDS.
- Recognize the clinical, imaging, and laboratory features of RDS.
- Recognize the pathologic features of RDS.
- Know the clinical strategies and therapies used to decrease the risk and severity of RDS.
- Know the management of RDS, including surfactant replacement.



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NeoReviews Quiz

10. Normal lung development during fetal life occurs through a series of sequential phases that leads to a mature lung with a large surface area and a minimal diffusion distance for gas exchange. Of the following, the presence of respiratory bronchioles, alveolar ducts, and primitive alveoli in the developing lung is *most* characteristic of the:
 - A. Alveolar phase.
 - B. Canalicular phase.
 - C. Embryonic phase.
 - D. Pseudoglandular phase.
 - E. Saccular phase.
11. In addition to phospholipids, pulmonary surfactant contains four major proteins: surfactant protein (SP)-A, SP-B, SP-C, and SP-D. Each surfactant protein has a specific function. Of the following, SP-B is *most* important for:
 - A. Facilitating formation of tubular myelin.
 - B. Participating in host innate immune defense.
 - C. Promoting adsorption and spreading of surfactant.
 - D. Regulating surfactant reuptake and recycling.
 - E. Regulating surfactant secretion and uptake.
12. Surfactant replacement therapy has been approved by the United States Food and Drug Administration for the treatment of respiratory distress syndrome (RDS) since 1990. Several other therapeutic approaches have been studied as possible adjunct treatments for RDS, as reviewed in meta-analyses published in the *Cochrane Database of Systematic Reviews*. Of the following, the *most* promising adjunct treatment for RDS in preterm infants is the administration of:
 - A. Antithrombin.
 - B. Digoxin.
 - C. Furosemide.
 - D. Inositol.
 - E. Thyroxin.

Core Concepts : Respiratory Distress Syndrome

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