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Respiratory Distress Syndrome of the Newborn

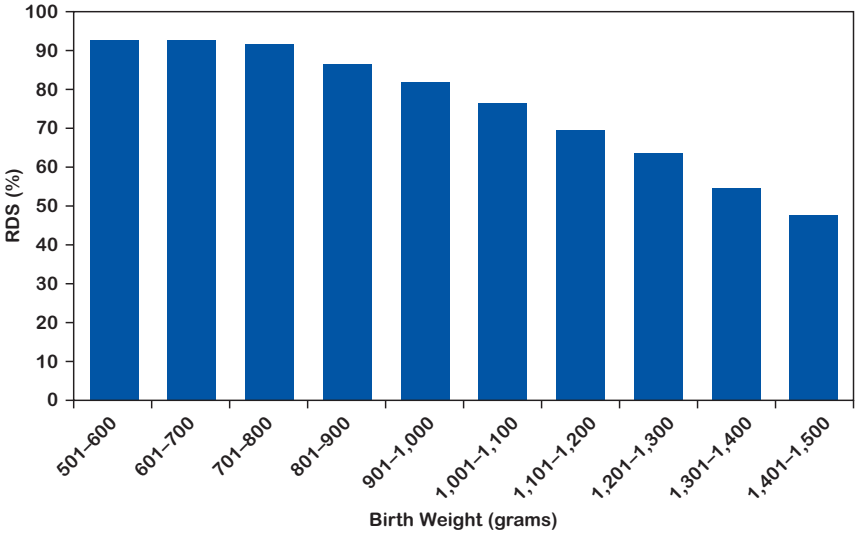
Respiratory distress syndrome (RDS) of the newborn, also known as *hyaline membrane disease*, is a breathing disorder of premature babies. In healthy infants, the alveoli—the small, air-exchanging sacs of the lungs—are coated by surfactant, which is a soap-like material produced in the lungs as the fetus matures in preparation for birth. If premature newborns have not yet produced enough surfactant, they are unable to open their lungs fully to breathe.

Whom does it affect?

Epidemiology, prevalence, economic burden, and vulnerable populations

Respiratory distress syndrome (RDS) affects about 1 percent of newborn infants and is the leading cause of death in babies who are born prematurely (1). About 12 percent of babies born in the United States are preterm, which is higher than in other developed countries (2). About 10 percent of premature babies in the United States develop RDS each year (3). The risk of RDS rises with increasing prematurity. Babies born before 29 weeks of gestation have a 60 percent chance of developing RDS (4), but babies born at full term rarely develop this condition. Maternal risk factors for preterm birth include previous preterm birth, periodontal disease, low maternal body mass, poor prenatal care, poverty, being uninsured, and being a member of a minority group (5).

Respiratory distress syndrome in the United States by birth weight



Incidence of respiratory distress syndrome (RDS) in the United States relative to birth weight, which shows it is a disease of premature infants. Horbar JD, Carpenter JH, Kenny M, eds. Vermont Oxford Network 2002 Very Low Birth Weight Database Summary. Burlington, VT: Vermont Oxford Network; 2003.

Among premature babies, the risk of developing RDS increases with Caucasian race, male sex, an older sibling with RDS, cesarean delivery, perinatal asphyxia, and maternal diabetes.

In 2003, the total number of live births in the United States for all races was 4,089,950; about 0.6 percent of newborns had RDS (about 24,000 or 6 per 1,000 live births) (6). In 2005, there were 4,138,000 live births in the United States, and a slightly larger number of babies were affected with RDS because the rate of premature births had increased from 11.6 percent to 12.7 percent, mainly due to a rise in late preterm births (34 to 36 weeks of gestation) (7).

Even though the number of RDS cases in the United States is growing, the infant mortality rate from RDS has dramatically declined from about 25,000 deaths per year in the 1960s to 860 deaths in 2005 (7) because of surfactant replacement therapy. Infant deaths from RDS were 2.6 times greater in African American babies than in Caucasian babies, although Caucasian babies are at a higher risk to develop the condition.

In 2001, hospital charges for a premature baby were estimated to be $75,000 (8). With approximately 18,000 hospitalizations each year due to

CASE STUDY

In August 1963, First Lady Jacqueline Bouvier Kennedy was hospitalized in her 34th week of pregnancy at the Otis Air Force Base Hospital. Her fetus was in distress, but labor did not progress. On August 7, she underwent a cesarean section to deliver Patrick Bouvier Kennedy, who weighed 4 pounds, 10.5 ounces (2,112 grams). After delivery, the baby developed difficulty breathing, which did not improve despite oxygen therapy. The baby was then rushed to Children's Hospital Boston, a leading center in respiratory distress syndrome (RDS). Unfortunately, despite the best medical efforts, the baby died two days later. The death of the newborn baby devastated the First Family. In the weeks that followed the tragedy, the president and his mother-in-law, Janet Auchincloss, feared that Jacqueline would have a nervous breakdown, although it was reported that this adversity ultimately brought the president and his wife closer together.

Comment

Although RDS affects the infant, in many ways, it takes a greater toll on the families. The newborn may be in a neonatal intensive care unit for a prolonged period, and the outcome is likely to be death or lifelong disability. The emotional, family, and economic stress can be ruinous. The story of the Kennedy child gripped the nation and alerted the world to the dire consequences of infant RDS. Patrick Kennedy's obituary in the New York Times *stated that the only treatment "for a victim of hyaline membrane disease is to monitor the infant's blood chemistry and to try to keep it near normal levels. Thus, the battle for the Kennedy baby was lost only because medical science has not yet advanced far enough to accomplish as quickly as necessary what the body can do by itself in its own time."*

RDS, the total cost of treating these babies in the hospital is approximately $2.3 billion.

What we are learning about the disease

Pathophysiology, causes: genetic, environment, microbes

Through the ages, infant death has been attributed to an inability of the newborn to adapt to life outside the uterus. In the early 20th century, "hyaline membranes"

were found during autopsy in the lungs of infants who died shortly after birth, but never in stillborns. In the 1920s, Dr. Kurt von Neergaard, a Swiss physiologist, postulated the existence of a substance in the lungs that reduces surface tension, allowing the lungs to open. In the 1950s, Dr. John Clements, a U.S. pulmonary physiologist, showed that this substance was surfactant. Finally, in 1959, Drs. Mary Ellen Avery and Jere Mead, both working at Harvard at the time, demonstrated that surfactant was lacking in the lungs of premature babies, which was the base cause of the respiratory failure seen in some of these infants (9).

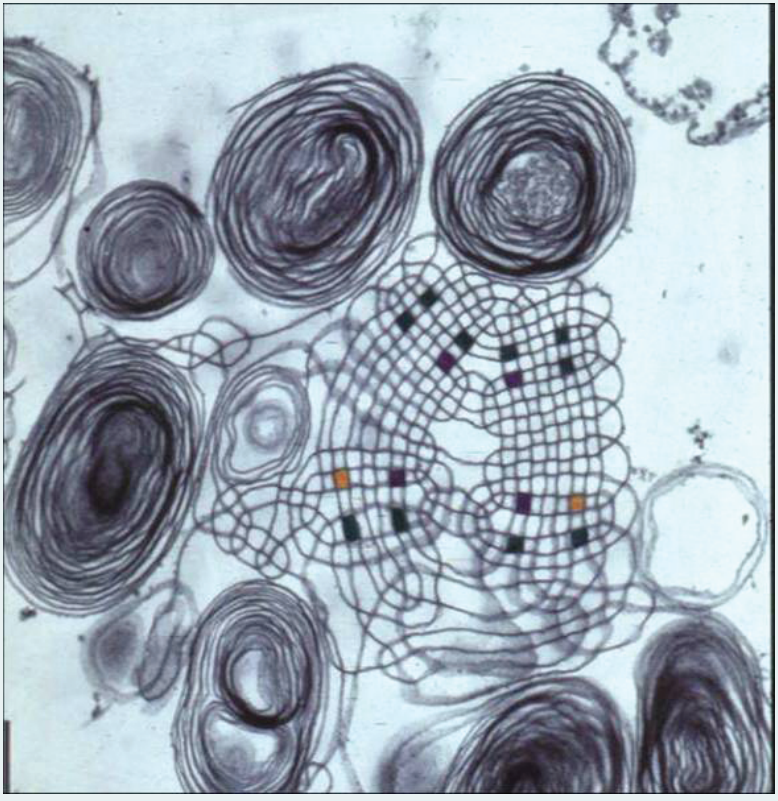
Further study on infant respiratory distress syndrome (RDS) found that the deficiency of surfactant was a consequence of either insufficient production by the immature lungs or a genetic mutation in one of the surfactant proteins, SP-B. The rarer genetic form of the disease is not associated with premature birth and occurs in full-term babies (10).

Surfactant is necessary for the tiny lung alveoli to overcome surface tension and remain open. Without adequate surfactant, the pressure exerted trying to open these alveoli by either the baby's desperate breathing or by a mechanical ventilator ruptures the alveoli, producing an emphysema-like picture, or pneumothorax, if the air escapes outside the lung and is trapped in the chest wall. Extremely premature babies may suffer from bleeding into the brain (intraventricular hemorrhage), sepsis, and other complications of their immature systems, including neurological and developmental damage. In survivors, bronchopulmonary dysplasia (a chronic scarring lung disease marked by prolonged oxygen need) may develop due to oxygen toxicity and mechanical ventilation. These complications are related to the severity of the disease, birth weight, and gestational age of the infant. Smaller babies are at greater risk of developing bronchopulmonary dysplasia.

How is it prevented, treated, and managed?

Prevention, treatment, prognosis

By far the biggest risk factor for respiratory distress syndrome (RDS) is prematurity. Preventing premature births could nearly eliminate RDS. Several causes of premature birth are preventable by good prenatal care. If the birth cannot be delayed beyond 34 weeks, the mother may be given corticosteroid therapy before birth, which accelerates fetal lung maturation. High-risk and premature infants require prompt attention by a pediatric resuscitation team. Healthcare providers



Steve Young

Without surfactant, breathing is impossible. Important basic science research led to the creation of surfactant replacement therapies that have dramatically improved survival of premature babies. However, there are still many mysteries about surfactant, including the function of this beautiful lattice-like structure; the colors were added to the squares of the lattice to help scientists understand how the lattices might form and work.

may deliver the baby and administer surfactant down the infant airways, either as soon as the premature baby is born or when RDS is diagnosed. The babies can be given respiratory support by mechanical ventilators with continuous positive airway pressure (CPAP) designed to prevent the alveoli from collapsing.

The use of oxygen has improved the life of many persons with respiratory disease. In the 1950s, however, its harmful effects were manifest when blindness occurred in premature infants given pure oxygen. As mechanical ventilation and

critical care became more sophisticated in the 1960s and 1970s, neonatal intensive care unit beds became filled with RDS survivors. Although these premature infants could be kept alive longer on ventilators, many still died, and those who lived often developed bronchopulmonary dysplasia.

One of the greatest breakthroughs in the fight against lung disease was the development of surfactant replacement therapy, which saves these premature infants from an almost certain death. Its use has led to a dramatic decrease in mortality from nearly 100 percent to less than 10 percent. Typically, infants are able to breathe more easily within a few hours of receiving surfactant, and complications such as lung rupture are less likely to occur. There is a risk of bleeding into the lungs from surfactant treatment, especially in extremely low birth weight infants (those weighing less than 1,000 grams).

In addition, inhaled nitric oxide can improve oxygenation and reduce pulmonary inflammation. When begun soon after birth in these premature infants, nitric oxide administration improves the acute disease and also reduces the chance of chronic lung disease. As with most drugs, it can also have side effects, including an increased risk of bleeding.

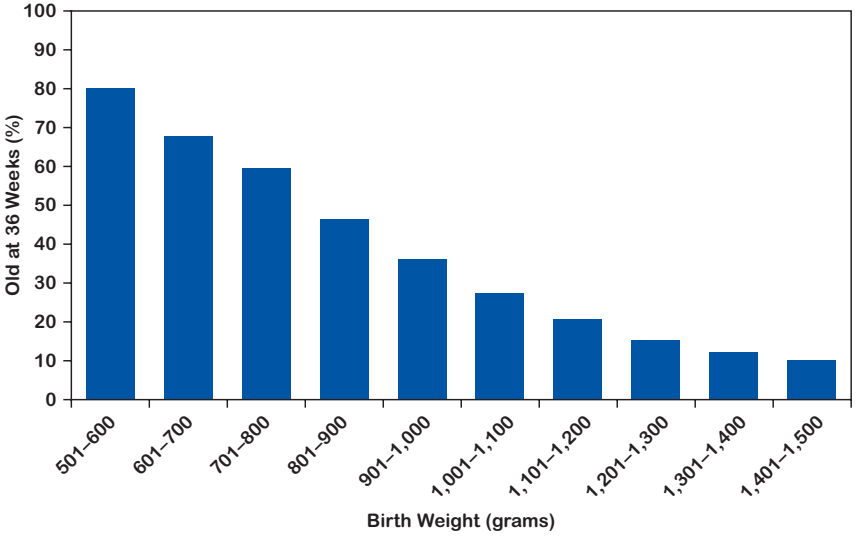
Are we making a difference?

Research past, present, and future

Although earlier research defined the disease, the major breakthrough came with the discovery that lack of surfactant was the main defect. Studying the physiology of lungs under different conditions showed how critical surfactant was for breathing. Further research into the production, function, and composition of surfactant produced a deeper understanding of respiratory distress syndrome (RDS). The race was then on to develop surfactant replacement therapy. Both synthetic and animal-derived substances as well as components of surfactant were investigated as possible therapies. By 1987, clinical studies with surfactant therapy had begun in Japan, and studies in animal models of RDS were under way in the United States. The use of surfactant derived from calf lung produced gratifying results when given immediately after birth. There were concerns that disease transmission could occur from treating newborns with an animal-derived product, but fortunately this has not been reported.

Currently, all of the surfactant replacement therapies in use in the United States are animal derived. The surfactant replacement material is not as

Chronic lung disease by birth weight



Incidence of bronchopulmonary dysplasia (BPD), defined as oxygen use at 36 weeks corrected postnatal age in premature babies. Horbar JD, Carpenter JH, Kenny M, eds. Vermont Oxford Network 2002 Very Low Birth Weight Database Summary. Burlington, VT: Vermont Oxford Network; 2003.

complete as natural human surfactant, and it is not effective in treating the type of RDS caused by the genetic mutation in SP-B, but for most cases, it has been wonderfully successful.

Despite the success of surfactant replacement in improving survival of premature babies with RDS, 5,000 to 10,000 newborns still develop bronchopulmonary dysplasia or other forms of chronic lung disease. The problem is most severe for the smallest babies in the extremely low birth weight group (500 to 699 grams), up to 85 percent of whom develop this complication. Preterm infants with bronchopulmonary dysplasia are at increased risk of death, re-hospitalization, and chronic and acute respiratory symptoms requiring therapy as compared with full-term infants. Therefore, recent research, both basic and clinical, has focused on efforts to prevent this complication. Clinical trials testing the usefulness of continuous nitric oxide inhalation therapy after birth and of repeated doses of surfactant to reduce the incidence and severity of bronchopulmonary dysplasia are ongoing.

Although there has been great reduction in the mortality and morbidity from RDS, the disease itself continues to increase with the rising rates of premature

births. Strategies, such as giving continuous positive airway pressure (CPAP), ventilating babies without intubation, and nitric oxide therapy without mechanical ventilation, are being tested to prevent complications of RDS.

Nutrition is important for normal lung development and maturation. Several studies have shown that poor nutrition (specifically, a lack of protein) after birth may increase risk of lung injury that can lead to bronchopulmonary dysplasia. Vitamin A, a nutrient important for cell growth, has been shown to decrease bronchopulmonary dysplasia in some studies. Other nutrients may provide premature infants with added protection against this condition.

Surfactant therapy and other medical and critical care advances have increased survival among extremely low birth weight infants. These advances have presented additional challenges because these extremely premature babies often survive with residual long-term complications of RDS. If complications during pregnancy indicate that a premature birth is likely, obstetricians can test the amniotic fluid for surfactant in order to track fetal lung development. Several tests are available that correlate with the production of surfactant.

What we need to cure or eliminate respiratory distress syndrome of the newborn

Respiratory distress syndrome (RDS) can be cured but not eliminated. The defect has been discovered. A treatment has been developed, and thousands of lives have been saved. Despite this, newborns still develop bronchopulmonary dysplasia. Part of the problem is that surfactant replacement therapy and other medical and critical care advances have allowed the survival of extremely premature infants, who may later have residual long-term complications of RDS. Preventing prematurity is probably now the most important factor in eliminating RDS. Understanding of and advancements in nutrition and the delivery of critical care medicine to newborns will also improve the outcome of those with this condition.

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Web sites of interest

National Heart, Lung, and Blood Institute
Diseases and Conditions Index
www.nhlbi.nih.gov/health/dci/Diseases/rds/rds_all.html

Centers for Disease Control and Prevention
National Center for Health Statistics
www.cdc.gov/nchs

American Lung Association
www.lungusa.org