Prevention and Treatment of Respiratory Distress Syndrome in Preterm Neonates

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The purpose of this column is to describe the pathophysiology of neonatal respiratory distress syndrome and the roles of antenatal corticosteroids and postnatal surfactant in prevention and treatment.

Accepted for publication
January 2018.

Abstract

Respiratory distress syndrome (RDS) impacts a high proportion of preterm neonates, resulting in significant morbidity and mortality. Advances in pharmacotherapy, specifically antenatal corticosteroids and postnatal surfactant therapy, have significantly reduced the incidence and impact of neonatal RDS. Antenatal corticosteroids accelerate fetal lung maturation by increasing the activity of enzymes responsible for surfactant biosynthesis, resulting in improved lung compliance. Maternal antenatal corticosteroid treatment has improved survival of preterm neonates and lowered the incidence of brain injury. After birth, exogenous surfactant administration improves lung compliance and oxygenation, resulting in reductions in the incidence of pneumothorax and of death. Future research will identify the optimal surfactant product, timing of the initial dose, and mode of delivery.

Keywords: antenatal corticosteroids; premature infant; pulmonary surfactants; RDS

The prevention and treatment of neonatal respiratory distress syndrome (RDS) represents both a remarkable success and persistent challenge in the care of neonates. The incidence of RDS is inversely proportional to gestational age with disease occurring in nearly all preterm neonates born at 22–28 weeks' estimated gestation, approximately 3 percent of late preterm neonates born at 34–36 weeks' gestation, and 0.12 percent of term neonates born at ≥37 weeks' gestation.[1–3] Among late preterm and term neonates, male sex and Caucasian ethnicity are associated with increased risk of RDS.[2] Experimental animal data suggest the sex difference may be because of androgen inhibition of surfactant production in males and estrogen acceleration of lung maturation and surfactant production in females.[4] Although the mechanism underlying the racial disparity in RDS has not been elucidated, genetic factors contribute to the development and severity of RDS.[5–7] Additional risk factors include elective delivery in the absence of labor and perinatal hypoxia-ischemia.[8] Also, maternal diabetes may increase RDS risk by producing fetal hyperglycemia and hyperinsulinism, which decrease synthesis and secretion of surfactant from alveolar Type II cells.[9–11]

The outcome of premature neonates with RDS has improved substantially over the past 50 years. In 1963, Patrick Bouvier Kennedy, the fourth child of President and Mrs. John F. Kennedy, was born prematurely at 34 weeks' gestation and died at two days of life from RDS. His course was not uncommon for the time, as the mortality rate of neonates with RDS was approximately 40 percent. Fifty years later, many neonates born as prematurely as 23 weeks' gestation with RDS survive[12]; however, RDS remains a leading cause of neonatal morbidity and mortality among neonates born in the United States.[13] The two major advances in obstetric and neonatal intensive care that have contributed to improved survival among neonates with

http://dx.doi.org/10.1891/0730-0832.37.3.169

RDS are antenatal corticosteroid administration to accelerate pulmonary maturity and postnatal surfactant replacement therapy.

PATHOPHYSIOLOGY

Neonatal RDS results from impaired or delayed production and secretion of pulmonary surfactant, a protein-phospholipid mixture that lowers surface tension at the air–liquid interface of the alveolus. Insufficient surfactant production or secretion results in higher alveolar surface tension, leading to atelectasis and impaired gas exchange. Surfactant phospholipids and proteins are synthesized in alveolar Type II cells, packaged into lamellar bodies (lysosome-related, specialized intracellular organelles), and released into the alveolar lumen via exocytosis. Within the alveolar lumen, lamellar bodies unravel to form tubular myelin, a lattice structure upon which phospholipids adsorb to create the interface between air and liquid.[14] Alveolar Type II cells differentiate during the canalicular stage of fetal lung development and lamellar bodies appear by approximately 22 weeks' gestation. Surfactant production increases in lung tissue until approximately 35 weeks' gestation.[15,16] Surfactant production is compromised by acidosis, cold stress, hypovolemia, and hypoxemia even in the setting of mature alveolar Type II cells. Postnatal exposures may also impact surfactant production. Specifically, invasive mechanical ventilation may result in exposure to high inspired oxygen concentrations, excess ventilatory pressures (resulting in barotrauma), and overdistention of the neonatal lung (resulting in volutrauma). These exposures trigger the release of proinflammatory cytokines and chemokines damaging the alveolar epithelial lining, resulting in impaired surfactant synthesis. Additionally, the leakage of fibrin and other proteins from the alveolar surface promotes surfactant inactivation.

The autopsies of neonates dying from RDS reveal a nearly uniformly airless lung. Microscopic examination reveals diffuse atelectasis surrounding a few widely dilated terminal bronchioles and alveolar ducts. A fibrinous eosinophilic membrane (or hyaline membrane) containing cellular debris derived from blood and injured epithelium lines these airspaces. This classic postmortem finding established the initial nomenclature for RDS as hyaline membrane disease.[17,18]

Immature pulmonary epithelial membrane transport proteins also contribute to the respiratory manifestations of surfactant deficiency. In utero, fluid follows chloride ions actively secreted into the alveolar spaces via sodium-potassium-chloride co-transporters and other cellular ion transporters.[19] These ion transporters are down-regulated in late gestation, slowing the accumulation of fetal lung fluid.[20,21] During labor, a rise in epinephrine levels induces sodium absorption via epithelial sodium channels and sodium-potassium-ATPase.[22] Maximal expression of epithelial sodium channels occurs in late gestation.[23,24] Hence, premature birth or delivery in the absence of labor can result in excess fetal lung fluid at birth; the inability to remove this fluid after birth can result in pulmonary edema which exacerbates respiratory distress.[25]

The initial hypoxemia from RDS secondary to surfactant deficiency will likely worsen without appropriate intervention. Decreased oxygen delivery to peripheral tissues results in anaerobic metabolism leading to generation of lactic acid. Acidosis prevents the natural dilation of the pulmonary vasculature after birth and can lead to the development of persistent pulmonary hypertension of the newborn. In this setting, right-to-left (pulmonary-to-systemic) shunting of deoxygenated blood from the pulmonary artery through the ductus arteriosus into the systemic circulation before oxygenation in the lungs perpetuates the cycle of hypoxemia and acidosis.

Uncomplicated RDS typically worsens for two to three days after birth before gradual recovery. Complications of RDS include development of air leaks (e.g., pneumothorax or pneumomediastinum), hemodynamically significant patent ductus arteriosus, pulmonary hemorrhage, intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD, defined as a requirement for supplemental oxygen at 36 weeks' corrected gestational age).

CLINICAL PRESENTATION

Although a definitive diagnosis of RDS requires pathologic or biochemical documentation of surfactant deficiency, clinicians commonly utilize a combination of clinical and radiographic features to diagnose RDS. Clinical symptoms present soon after birth and include tachypnea, grunting, subcostal and intercostal retractions, nasal flaring, and cyanosis. In severe cases of RDS, neonates may progress to respiratory failure requiring intubation and mechanical ventilation.

The chest radiograph reveals a diffuse, symmetric, reticulogranular pattern in the peripheral lung fields, mimicking the appearance of ground glass. This pattern results from the combination of alveolar atelectasis and pulmonary edema. Superimposed air bronchograms, or large bronchioles filled with air surrounded by small collapsed alveoli, can be seen. In severe cases, complete opacification or "white-out" of the lungs may be observed.

PREVENTION

Widespread utilization of antenatal corticosteroids in cases of impending preterm delivery has substantially reduced the mortality associated with neonatal RDS. Examining the impact of corticosteroids on premature delivery in 1969, Liggins observed the absence of RDS in exposed premature lambs.[26] Antenatal corticosteroids at levels mimicking physiologic stress accelerate fetal lung maturation by increasing the activity of enzymes responsible for surfactant biosynthesis.[27] Physiologic and morphometric measurements suggest structural lung maturation accompanies the increased alveolar surfactant pool size.[28] Clinically, these physiologic and structural changes result in improved lung compliance.

In 1972, Liggins and Howie published the first prospective, blinded, controlled trial of antenatal betamethasone treatment in mothers at risk of premature delivery.[29] The results of this trial and others (30 total trials including 8,158 infants) have demonstrated a reduction in the incidence of RDS in neonates born before 34 weeks' gestation after treatment with antenatal corticosteroids (risk ratio [RR] 0.66, 95% confidence interval [CI] 0.56–0.77, number needed to treat [NNT] 17) and improvement in neonatal survival (RR of death 0.69, 95% CI 0.59–0.81, NNT 36).[30] Additional benefits to the neonate include a reduction in the incidences of IVH (RR 0.55, 95% CI 0.40–0.76, NNT 46) and necrotizing enterocolitis (RR 0.50, 95% CI 0.32–0.78, NNT 87).[30,31]

The risks of corticosteroids to the mother and neonate appear to be minimal. Although there have been concerns regarding the impact of antenatal corticosteroids on the incidence of postnatal infection, studies in the setting of prolonged rupture of membranes suggest no impact on the incidence of maternal or neonatal infection.[32] Antenatal corticosteroids may increase total leukocyte and immature neutrophil counts in neonates; this should be considered in the clinical evaluation of early onset neonatal sepsis.

Although corticosteroids have been routinely given to mothers who are at risk of preterm delivery at less than 34 weeks' gestation for over two decades, more recently, benefits from antenatal corticosteroids have also been observed in late preterm neonates born at 34–36 weeks' estimated gestation. In a recent, large, randomized controlled trial of 2,827 late preterm neonates, antenatal betamethasone therapy reduced the need for resuscitation at birth (14.5 percent vs 18.7 percent, $p = .003$), postnatal surfactant therapy (1.8 percent vs 3.1 percent, $p = .004$), and prolonged continuous positive airway pressure (CPAP) or high-flow nasal cannula (11.6 percent vs 14.4 percent, $p = .02$).[33] Late preterm neonates who were exposed to antenatal steroids had an increased incidence of hypoglycemia (<40 mg/dL [<2.2 mmol/L]) and careful blood glucose monitoring is recommended for these neonates.[34]

Current guidelines recommend a single course of antenatal corticosteroids be administered to all mothers at risk of preterm delivery between 24 and 33 6/7 weeks' gestation.[35] Antenatal steroids should be considered for women between 34 and 36 6/7 weeks' gestation who are at risk of preterm birth within the next seven days and have not previously received corticosteroids to accelerate fetal lung maturity.[35] The optimal corticosteroid (betamethasone or dexamethasone) has not been elucidated and requires further investigation.[36] The optimal window for corticosteroid administration is 24 hours to seven days before birth. Administration before or after this window does produce benefit compared to no therapy.[37,38] Administration of a rescue course of corticosteroids is currently recommended for a woman at risk of preterm delivery before 34 weeks' gestation whose previous course was received more than 14 days prior.[35,39] Concerns exist regarding fetal brain and lung growth as well as adrenal suppression. However, studies assessing children exposed to repeat courses of antenatal corticosteroids find no difference regarding physical or neurologic outcome at two years of age.[40] On this basis, the benefits of repeat courses warrant individual consideration.

TREATMENT

Nonpharmacologic Treatment

Appropriate treatment of neonatal RDS requires optimal respiratory support provided by an experienced multidisciplinary medical care team. Airway and alveolar expansion must be maintained to ensure adequate oxygenation and ventilation, often through the exogenous delivery of distending pressure. The desire to avoid the pulmonary damage associated with invasive mechanical ventilation has led to the extensive study of noninvasive CPAP in premature neonates with RDS. The value of CPAP in the absence of exogenous surfactant therapy remains an area of active research (see discussion regarding timing of surfactant therapy). Regardless of the method of respiratory support, diligent monitoring of gas exchange through measurement of blood gases is essential in neonates with RDS. Generally, goal arterial blood gas parameters include a pH of 7.25–7.35, $PaCO_2$ of 40–55 mmHg, and PaO_2 of 50–80 mmHg.

Surfactant

The discovery of surfactant and the development of surfactant products for exogenous administration have substantially improved morbidity and mortality in neonates with RDS. In 1929, von Neergaard filled a porcine lung with isotonic solution to evaluate the impact of surface tension on air–tissue interfaces. His experiment demonstrated that surface tension is largely responsible for lung recoil.[41] In the 1950s, Avery and Mead demonstrated that lung extracts from neonates who died of RDS had reduced surface tension and a deficiency of pulmonary surfactant.[18] The 1963 death of Patrick Kennedy raised public awareness of RDS and drove research of potential treatments. Initial studies administered artificial phospholipids via aerosol to neonates with RDS with disappointing results.[42] Subsequent preclinical experiments demonstrated improved oxygenation and lung compliance utilizing natural surfactant derivatives administered by endotracheal instillation. In 1980, Fujiwara and colleagues developed a mixture of natural and synthetic surface-active lipids for use in human neonates, resulting in the survival of eight of ten preterm neonates with severe RDS (gestational ages 28-33 weeks).[43] Controlled trials of numerous surfactant products were conducted in the 1980s before the U.S. Food and Drug Administration (FDA) approval of colfosceril palmitate (Exosurf), a protein-free synthetic surfactant, in 1990. Colfosceril palmitate is no longer marketed because of clinical inferiority to natural surfactant products. Three natural surfactant products have received FDA approval: beractant (Survanta) in 1991, calfactant (Infasurf) in 1998, and poractant alfa (Curosurf) in

TABLE 1 ■ Comparison of Exogenous Surfactant Products

Surfactant	Source	Components	Phospholipid Concentration (%)	Dose (mg/kg)	Dose (mL/kg)	Frequency (in Hours)	Maximum Number Of Doses
Colfosceril palmitate (Exosurf)	Synthetic	Phospholipids	1.35	67.5	5	Every 12	2
Beractant (Survanta)	Minced bovine lung extract	Phospholipids, SP-B (<0.1%), SP-C	2.5	100	4	Every 6–12	4
Calfactant (Infasurf)	Calf lung lavage	Phospholipids, SP-B (0.26 mg/mL), SP-C	3.5	100	3	Every 12	3
Poractant alfa (Curosurf)	Minced porcine lung extract	Phospholipids, SP-B (0.2 mg/mL), SP-C	7.6	200	Initial: 2.5 Repeat: 1.25	Every 12	3
Lucinactant (Surfaxin)	Synthetic	Phospholipids, 0.1 mg/mL sinapultide (synthetic SP-B)	3	174	5.8	Every 6–12	4

1998. In 2012, lucinactant (Surfaxin), a synthetic surfactant containing protein, received FDA approval (Table 1).

Structure and Function of Surfactant. Surfactant is composed of phospholipids, neutral lipids, and surfactant proteins (Figure 1). The phospholipid component is comprised mainly by dipalmitoyl phosphatidylcholine (DPPC), which has a hydrophilic head and hydrophobic tail and reduces surface tension at the air–liquid interface of the alveolar surface, lowering the pressure required to maintain lung expansion during the respiratory cycle (Figure 2).[44] Additional phospholipids in pulmonary surfactant include phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, and phosphatidylethanolamine.

Surfactant proteins A, B, C, and D compose a small percentage of the weight of natural surfactant. However, they serve vital functions, including facilitation of phospholipid spreading and adsorption *in vivo*. Surfactant protein A (SP-A) regulates pulmonary surfactant turnover, contributes to immune function, and is necessary for the formation of tubular myelin.[45] Surfactant protein B (SP-B) is also essential to the formation of tubular myelin. SP-B is highly hydrophobic and the major surfactant

FIGURE 1 ■ Composition of pulmonary surfactant.

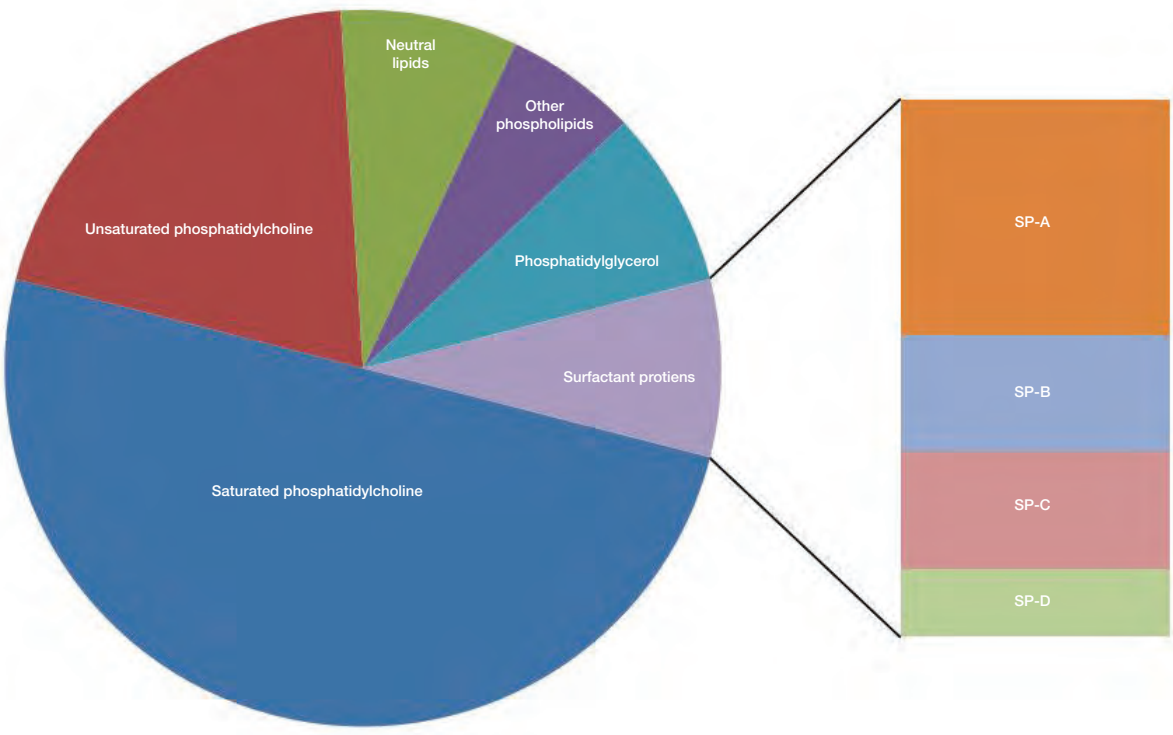
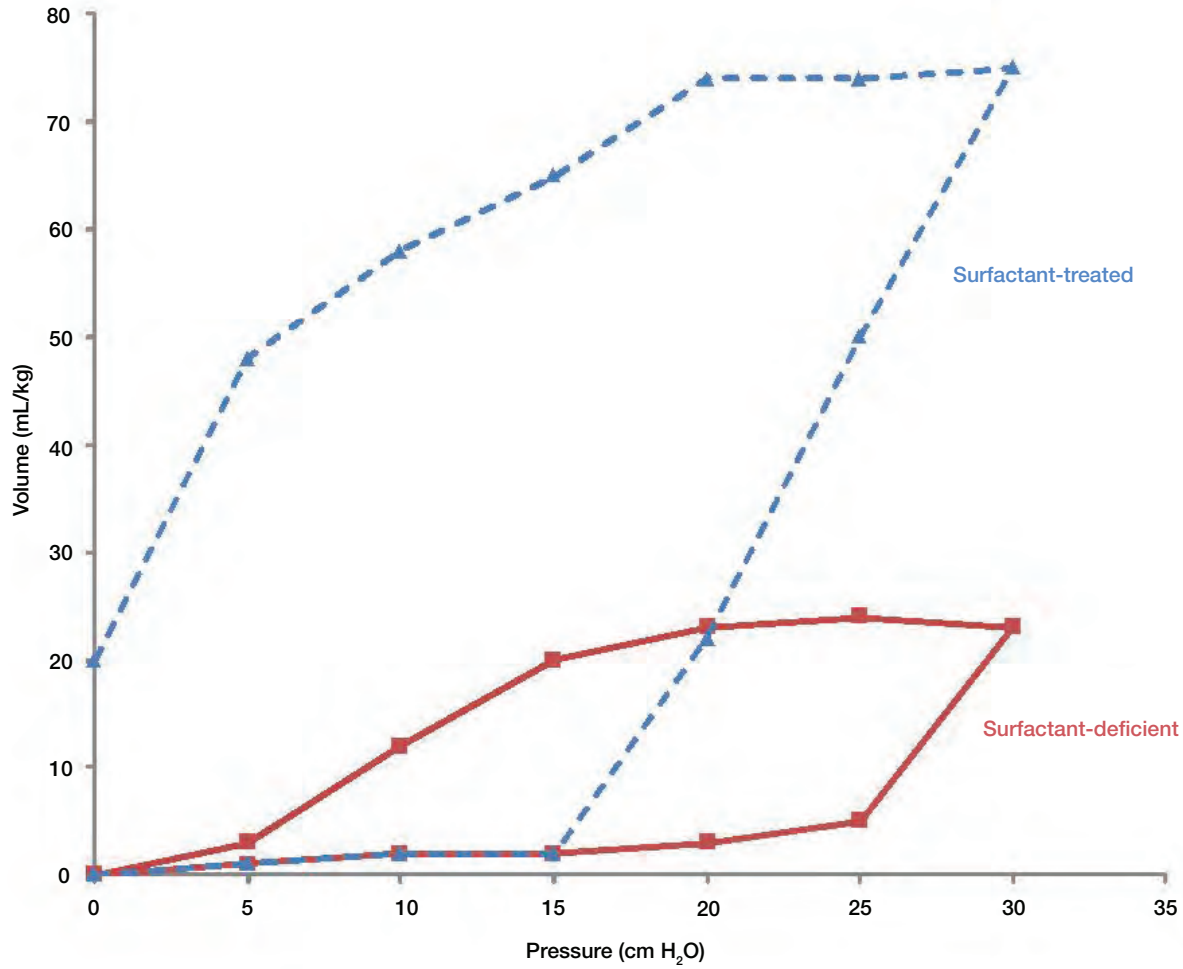


FIGURE 2 ■ Pressure–volume relationship for the inflation and deflation of a surfactant-deficient and surfactant-treated lung.



Adapted from Rider ED, Jobe AH, Ikegami M, Sun B. Different ventilation strategies alter surfactant responses in preterm rabbits. *J Appl Physiol.* 1992;73:2089–2096.

component responsible for stabilizing the phospholipid layer laterally. Additionally, SP-B facilitates resistance to inactivation of surfactant by substances including meconium and serum.[46] Recessive loss of function mutations in the gene encoding SP-B result in lethal respiratory distress.[47] Surfactant protein C (SP-C) increases adsorption of DPPC and other phospholipids to the air–liquid interface.[46] Infants and children with dominant mutations in the gene encoding SP-C can present with interstitial lung disease, and more rarely with neonatal RDS.[48] Surfactant protein D (SP-D) is composed of lectins, suggesting a role in bacterial opsonization and host lung defense.[45]

Efficacy. Initial trials of the synthetic surfactant preparation colfosceril palmitate demonstrated significant reductions in the incidence of pneumothorax and mortality.[49] However, natural surfactants demonstrate superiority when compared to colfosceril palmitate, emphasizing the essential role of proteins to surfactant function (Table 2).[50] Despite its impact on mortality, surfactant administration does not consistently reduce the incidence of other morbidities associated with preterm birth, including IVH and BPD. These findings may be explained by increased survival in very preterm neonates at highest risk of these comorbidities. However, natural surfactant therapy reduces the composite incidence of death or severe disability at one year of age.[51]

The comparison of efficacy among natural surfactants provides unique challenges and produces ongoing debate. Numerous randomized trials comparing standard doses of beractant with calfactant and beractant with poractant alfa have found no significant differences in mortality or BPD between therapies.[52] A large retrospective analysis by Trembath and colleagues (N = 51,282 neonates) failed to confirm any mortality difference between the available natural surfactant products.[53] A randomized trial of calfactant and

TABLE 2 ■ Relative Risks of Potential Beneficial Effects of Exogenous Surfactant Therapy[49,50,55]

	Prophylaxis			Rescue		
Outcome	First Generation Synthetic vs Placebo	Natural vs First Generation Synthetic	Second Generation Synthetic vs Natural	First Generation Synthetic vs Placebo	Natural vs First Generation Synthetic	Second Generation Synthetic vs Natural
Pneumothorax	0.64 (0.49–0.89)	0.70 (0.46–1.07)	1.00 (0.73–1.37)	0.52 (0.42–0.65)	0.64 (0.53–0.77)	–
IVH	0.94 (0.73–1.21)	1.13 (1.00–1.27)	1.01 (0.88–1.15)	0.95 (0.73–1.24)	1.03 (0.94–1.14)	–
BPD	1.09 (0.80–1.47)	1.01 (0.89–1.15)	0.99 (0.84–1.18)	0.88 (0.67–1.17)	0.98 (0.86–1.11)	–
Death	0.67 (0.52–0.88)	0.93 (0.77–1.13)	0.79 (0.61–1.02)	0.60 (0.42–0.85)	0.86 (0.75–0.99)	–

Abbreviations: BPD = bronchopulmonary dysplasia = oxygen requirement at 36 weeks' postmenstrual age; IVH = intraventricular hemorrhage.

high-dose poractant alfa may be useful to supplement the lack of direct comparisons of these surfactant products.

Lucinactant, a novel synthetic surfactant, represented an additional therapeutic alternative.[54] Preclinical studies suggested improved resistance to inactivation by serum proteins and reactive oxygen species because of the presence of sinapultide, a synthetic peptide with similar activity to SP-B. Additionally, the synthetic nature allows avoidance of animal product exposure. Two clinical trials, including a total of 1,028 preterm neonates, demonstrated equivalence between lucinactant and natural surfactants and led to U.S. FDA approval in 2012 (see Table 2).[55] Practical concerns existed, including the larger volume standard dose, the requirement for warming and cooling before administration, and limited stability after warming. Limited adoption in clinical practice led to market withdrawal in 2015.

Adverse Effects. Administration of exogenous surfactant can result in transient airway obstruction, potentially leading to oxygen desaturation and bradycardia. The airway obstruction may be severe enough to induce changes in cerebral blood flow velocity, increasing the risk of IVH.[56] The association between surfactants and periventricular leukomalacia, a form of white matter brain injury common in premature neonates, remains controversial. The proposed mechanism for this finding is a rapid increase in compliance leading to overventilation and hypocarbia, which reduces cerebral blood flow. Diligent respiratory monitoring and ventilator adjustment to avoid hypocarbia may mitigate this effect. An association between surfactant administration and pulmonary hemorrhage has also been reported.[57] This adverse effect likely results from improvements in lung compliance and oxygenation that promote pulmonary vasodilation and left-to-right shunting through the ductus arteriosus. The resultant increase in pulmonary blood flow may produce pulmonary congestion and increased alveolar capillary pressure. Rupture of these capillaries results in intra-alveolar hemorrhagic pulmonary edema.

Administration. Surfactant products should be stored in a refrigerator and protected from light until ready for use. Natural surfactants should be allowed to warm to room temperature before administration. The natural surfactant suspension should be gently swirled, but not shaken, to ensure complete dispersion before administration. Unopened vials warmed to room temperature may be returned to the refrigerator once within 8 hours (beractant) or 24 hours (calfactant and poractant alfa) for future use. Traditionally, the surfactant suspension is instilled into the neonate's endotracheal tube. The total dose should be administered in two to four aliquots with careful attention paid to infant positioning to ensure symmetric distribution. Ventilation and positive end expiratory pressure should be maintained during surfactant administration by an experienced clinician. Adjustment of mechanical ventilator settings during and after surfactant administration is required as the pulmonary compliance of the neonate may improve markedly.

In an effort to reduce barotrauma associated with positive pressure ventilation and mitigate several adverse effects discussed previously, clinicians have developed less-invasive methods of surfactant administration.[58] In a randomized controlled trial of 220 extremely preterm neonates, administration of surfactant via a thin plastic catheter guided by laryngoscopy resulted in a decreased need for mechanical ventilation; however, there were no differences in mortality or the incidence of BPD.[59] Additional studies may clarify the risks and benefits of this approach, including the technical feasibility of more widespread utilization.

Timing of the Initial Surfactant Dose. Traditionally, administration of surfactant early in the course of respiratory distress (<2 hours of life) has been preferred. Earlier dosing provides superior lung dispersion and minimizes the duration of mechanical ventilation. Meta-analyses of trials comparing early versus delayed (two or more hours after birth) surfactant administration in preterm neonates requiring mechanical ventilation demonstrate decreased risk of pneumothorax and pulmonary interstitial emphysema with early administration.[60] Early administration reduces neonatal mortality and BPD.[60] Consequently, neonates born at less than 30 weeks' estimated gestation requiring endotracheal intubation for RDS should receive early surfactant therapy.[61]

However, routine application of CPAP in the delivery room has facilitated consideration of prophylactic versus

rescue surfactant therapy in preterm neonates. In populations with widespread antenatal corticosteroid use and routine provision of optimal noninvasive CPAP in the delivery room, up to 17 percent of extremely preterm neonates 24–27 weeks' estimated gestation and approximately 50 percent of neonates born at 26–30 weeks' gestational age do not require invasive mechanical ventilation or surfactant.[62,63] With increased utilization of antenatal corticosteroids and routine post-delivery stabilization on CPAP, a strategy of early selective surfactant administration to neonates requiring intubation reduces the risk of BPD and death as compared to routine prophylactic surfactant administration.[64]

Single vs Multiple Doses. Neonates with established RDS may benefit from multiple doses of surfactant. Randomized trials of multiple dose strategies demonstrate a reduced incidence of pneumothorax and a trend toward reduced mortality compared to single dose administration.[65] Criteria for clinically indicated repeat dosing are highly variable. Most commonly, neonates receive subsequent doses of surfactant at 12-hour intervals for increased inspired oxygen >40 percent. A maximum of three additional doses of beractant and two additional doses of calfactant or poractant alfa should be administered in the first 48 hours of life.

Trials of late surfactant administration have produced mixed results. A randomized controlled trial of 511 extremely preterm newborns given calfactant or placebo every one to three days to a maximum of five doses while intubated demonstrated no difference in the incidence of BPD or death at 36 weeks' postmenstrual age.[66] A smaller randomized controlled trial of poractant alfa versus placebo in 118 preterm neonates who required mechanical ventilation at 14 days of life produced similar short-term outcomes.[67] However, this trial documented a reduced incidence of rehospitalization for respiratory complications after discharge in treated neonates (28.3 percent vs 51.1 percent, $p = .03$). Long-term follow-up of the larger trial will inform the inception and design of future trials of late surfactant administration.

CONCLUSION

The outcome of neonates with RDS has substantially improved over the past 50 years, in large part because of the widespread utilization of pharmacologic prevention and treatment strategies. Antenatal corticosteroids facilitate pulmonary maturation in the setting of impending preterm birth. After birth, preterm neonates benefit from exogenous surfactant therapy. Despite substantial progress, mortality and morbidities are still common among preterm neonates. Continued research will improve both survival and quality of life in these children.

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