



Surfactant Replacement Therapy*

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Surfactant replacement therapy (SRT) has a proven role in the treatment of neonatal respiratory distress syndrome and severe meconium aspiration syndrome in infants, and may have a role in the treatment of pediatric patients with ARDS. Although newer delivery mechanisms and strategies are being studied, the classic surfactant administration paradigm consists of endotracheal intubation, surfactant instillation into the lung, and stabilization with mechanical ventilation followed by extubation when stable on low respiratory support. Currently, this surfactant administration procedure is bundled into Current Procedural Terminology (CPT) codes used when providing intensive care. A specific CPT code for surfactant administration is scheduled to be introduced in 2007. This article reviews clinical issues in SRT and the practice management considerations necessary to provide this care.

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Key words: neonatology; respiratory failure; surfactant

Abbreviations: ALI = acute lung injury; CDH = congenital diaphragmatic hernia; CI = confidence interval; CPAP = continuous positive airway pressure; CPT = Current Procedural Terminology; ECMO = extracorporeal membrane oxygenation; FDA = Food and Drug Administration; MAS = meconium aspiration syndrome; RCT = randomized controlled trial; RDS = respiratory distress syndrome; RR = relative risk; SP = surfactant protein; SRT = surfactant replacement therapy

On August 7, 1963, Patrick Bouvier Kennedy, infant son of President and Mrs. John F. Kennedy, was born prematurely at 33 weeks gestation. Two days later, Patrick died of the most common complication of premature birth, respiratory distress syndrome (RDS). Occurring just 4 years after Avery and Mead¹ first reported an association between RDS and surfactant deficiency, the death of Patrick Kennedy inspired aggressive research into the cause and treatment of RDS and served as a catalyst in the development of regionalized neonatal

intensive care. Research efforts led to the first report in 1980 of exogenous surfactant replacement therapy (SRT) to treat RDS,² and culminated with US Food and Drug Administration (FDA) approval in 1990 of the first exogenous surfactant drug (Exosurf [colfosceril palmitate HSE]; Glaxo Wellcome; Uxbridge, Middlesex, UK). SRT remains an active research area, with the publication of > 85 articles since 2000, including 34 new randomized controlled clinical trials (RCTs) of SRT for the treatment of infants with RDS.³ This article will review SRT in infant, pediatric, and adult patients, and will discuss the practice management of SRT for the physicians caring for these populations.

SURFACTANT METABOLISM, COMPOSITION, AND FUNCTION

Pulmonary surfactant is synthesized by type II pneumocytes, is stored in lamellar bodies, and is secreted into the airspace as tubular myelin, from which it is then adsorbed into the air-water interface to form a surfactant monolayer. Pulmonary surfactant is composed of 80% phospholipids, 8% neutral lipids, and 12% proteins, including proteins from

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plasma and lung tissue, as well as four surfactant-related proteins. Physiologically effective pulmonary surfactants have the following three essential behaviors: the ability to lower surface tension; the ability to be adsorbed into air-water interfaces; and the ability to dynamically spread and respread along the air-water interface during tidal volume breathing as the alveolar surface stretches and contracts.⁴ While the phospholipid components of natural surfactant, especially dipalmitoyl phosphatidylcholine, are the most surface-active agents and are primarily responsible for lowering alveolar surface tension, surfactant-related proteins play critical roles in surfactant surface behaviors as well as in immune defense and particle clearance.

Surfactant protein (SP)-A and SP-D are hydrophilic oligomers that are members of the collectin family of host defense proteins, playing a role in the immune response to microbial challenge by binding microorganisms and modulating leukocyte functions such as chemotaxis, cytokine function, and phagocytosis. SP-A is the most abundant of the SPs and facilitates the formation of aqueous surfactant aggregates, including tubular myelin. SP-D is not directly involved in the biophysical properties of lung surfactant but may play a role in surfactant reuptake and recycling. SP-B and SP-C are critically important small hydrophobic apoproteins that promote adsorption and dynamic spreading of surfactant to form a phospholipid monolayer that lines the alveolus. Congenital SP-B deficiency is a lethal cause of respiratory distress, while congenital SP-C deficiency is associated with chronic interstitial lung disease.

EXOGENOUS SURFACTANT PREPARATIONS

Surfactant drugs differ in both phospholipid and protein content and can be categorized as listed in Table 1. Although a complete description of individual surfactant preparations is beyond the scope of this review, differences between classes of surfactants can be briefly summarized. Synthetic surfactants differ most notably from natural surfactants in their protein composition. The original commercially available surfactant, colfosceril palmitate (Exosurf; Glaxo Wellcome), is composed of the phospholipid dipalmitoyl phosphatidylcholine and chemical agents to promote adsorption and spreading; it lacks SPs.

Natural surfactants are derived from animal lungs through a process of organic extraction from either the lipid component of minced lung tissue or from alveolar lavage fluid. SP-A, SP-B, SP-C, and SP-D are present in natural surfactant, and convey dramatic benefits on the ability of natural surfactant to lower alveolar surface tension and modulate lung

Table 1—Surfactant Preparation and Their Source*

Animal-derived surfactants	
Lung lavage	
	Alveofact (bovactant/bovine/Boehringer Ingleheim; Bilberach, Germany)
	BLES (BLES/bovine/BLES Biochemicals; London, ON, Canada)
	Infasurf (calfactant/bovine/ONY, Inc; Amherst, NY)
Processed animal lung tissue	
	Curosurf (poractant/porcine/Chiesi Farmaceutici SpA; Parma, Italy)
Supplemented, processed animal lung tissue	
	Surfacten (surfactant TA/bovine/Mitsubishi; Tokyo, Japan)
	Survanta (beractant/bovine/Abbott Laboratories; Abbott Park, IL)
Synthetic and recombinant lung surfactants	
Protein-free	
	ALEC (pumactant/Britannia Pharmaceuticals; Crawley, UK)
	Exosurf (colfosceril palmitate/Glaxo Wellcome; Uxbridge, Middlesex, UK)
Peptide-containing	
	Surfaxin (lucinactant/DiscoveryLabs; Warrington, PA)
Recombinant apoproteins	
	Recombinant SP-C surfactant

*Information is displayed as trade name (generic name/animal source, if applicable/manufacturer name and location).

inflammation *in vitro*. In clinical trials,⁵ natural surfactants have been shown to reduce the risk of pneumothorax more effectively than synthetic surfactant preparations.

Among natural surfactants, Survanta (Abbott Laboratories; Abbott Park, IL), Infasurf (ONY, Inc; Amherst, NY), and Curosurf (Chiesi Farmaceutici SpA; Parma, Italy) are approved for the treatment and prevention of RDS in infants. Although they contain foreign proteins, natural surfactant preparations have not triggered significant allergic responses in treated infants. In 2005, a new-generation synthetic surfactant, Surfaxin (DiscoveryLabs; Warrington, PA), using a novel peptide (KL4) to replace the biophysical properties of natural SPs, received favorable review by the FDA as a treatment for RDS. Final approval is pending.

SRT IN NEONATES

Exogenous surfactant therapy has an established role in the management of RDS. SRT reduces the incidence of death, air leak syndromes, and intraventricular hemorrhage in premature infants. The optimal patient population and timing of surfactant delivery remains controversial. SRT for the treatment of RDS can be divided into the following two broad treatment strategies based on the time of delivery: prophylactic; and, later, selective surfactant administration.

Prophylactic therapy offers the advantage of rapidly establishing normal surfactant pools and improving lung mechanics, thus preempting the influx of protein-containing fluid that occurs as the result of the increased work of breathing and deleterious effects of oxygen and mechanical ventilation. The disadvantage of prophylactic surfactant administration is that an infant in whom RDS may not develop may be intubated and may receive a drug that may not be necessary. Selective surfactant therapy avoids the risk of overtreatment by treating only those infants with symptoms of RDS. The disadvantage of selective surfactant therapy is that delayed administration of surfactant allows lung inflammation and protein-containing fluid influx to impair gas exchange further before therapy is provided.

Infants at Risk for RDS

Prophylactic surfactant is administered to infants who are considered to be at high risk of developing RDS. The risk of RDS increases with decreasing gestational age (Fig 1).⁶ Factors such as maternal diabetes mellitus, white race, male sex, asphyxia, and sepsis increase the risk of RDS, while antenatal steroids and prolonged rupture of membranes decrease the risk. Overall, there is at least a 60% chance of RDS developing in infants of < 29 weeks gestation.

Prophylactic surfactant has been well studied, with at least eight randomized clinical trials enrolling > 2,500 premature infants. In a metaanalysis of these studies,⁷ prophylactic surfactant administered within 30 min after birth to infants who are at high risk for RDS compared to later selective treatment at the time of respiratory failure is associated with significant reductions in the risk of pneumothorax (relative risk [RR], 0.62; 95% confidence interval

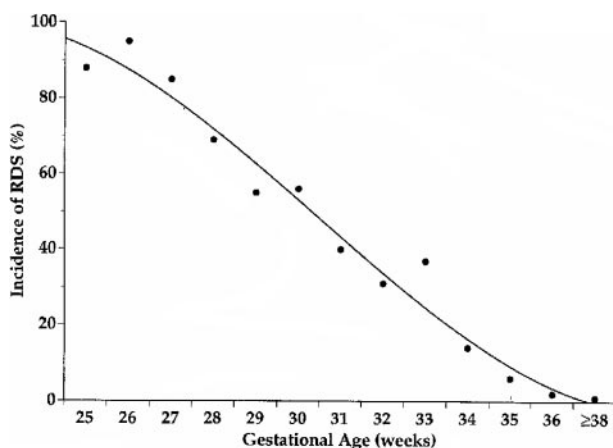


FIGURE 1. Incidence of RDS decreases with increasing gestational age.⁶

[CI], 0.42 to 0.89), pulmonary interstitial emphysema (RR, 0.54; 95% CI, 0.36 to 0.82), death (RR, 0.61; 95% CI, 0.48 to 0.77), and grade 3 or 4 intraventricular hemorrhage (RR, 0.19; 95% CI, 0.07 to 0.54). Although the metaanalysis does not show a reduction in the overall risk of bronchopulmonary dysplasia among survivors (defined as a need for mechanical ventilation or oxygen at 28 days of age), the risk of death or bronchopulmonary dysplasia among infants of < 30 weeks gestation was reduced (RR, 0.87; 95% CI, 0.77 to 0.97).⁷ Prophylactic surfactant is considered to be safe with treated patients and control subjects having similar rates of necrotizing enterocolitis, retinopathy of prematurity, and patent ductus arteriosus.⁷ In long-term neurodevelopmental follow-up, surfactant therapy in the neonatal period is not associated with increased rates of neurologic impairment.^{8,9} Based on the metaanalysis, the number needed to treat with prophylactic surfactant to prevent one death is 7, making prophylactic surfactant one of the most effective therapies in neonatology.

Prophylactic nasal continuous positive airway pressure (CPAP) (*ie*, CPAP started from the first breath in the delivery room) has been proposed as an alternative to prophylactic surfactant. Data from RCTs comparing the use of prophylactic nasal CPAP vs prophylactic surfactant are not available. Large RCTs are ongoing, and data should be available in the next few years.

Infants With RDS

Early Treatment vs Later Rescue Therapy: For infants who are at less of a risk for RDS, such as those born later than at 28 to 30 weeks gestation, prophylactic treatment with surfactant may result in overtreatment in $\geq 35\%$ of patients (Fig 1). For these infants, selective surfactant therapy, either early in the course of RDS or at the time of respiratory failure is appropriate. A regimen using multiple doses of surfactant, if required, has advantages over a single-dose regimen.¹⁰ Selective surfactant therapy may be subdivided into two strategies, early and delayed surfactant replacement. Early surfactant administration is provided to symptomatic infants within the first few hours after birth, shortly after the onset of respiratory symptoms, often before need for endotracheal intubation to treat respiratory failure. Later surfactant therapy is defined as surfactant administration at or near the time of respiratory failure when the newborn requires intubation and mechanical ventilation to maintain oxygenation. Early selective surfactant therapy compared with later therapy offers the advantage of restoring surfactant pools before lung inflammation and protein-

containing fluid influx inactivate native surfactant causing worsening gas exchange.

In a systematic review of studies comparing early vs late surfactant administration, early SRT decreased neonatal mortality (RR, 0.87; 95% CI, 0.77 to 0.99), pneumothorax (RR, 0.70; 95% CI, 0.59 to 0.82), and pulmonary interstitial emphysema (RR, 0.63; 95% CI, 0.43 to 0.93). In addition, the incidence of chronic lung disease or death at 36 weeks postmenstrual age was reduced (RR, 0.84; 95% CI, 0.75 to 0.93).¹¹

Infants With Meconium Aspiration Syndrome

Although it is becoming less frequent, meconium aspiration syndrome (MAS) is still a major cause of morbidity among term infants. Meconium aspiration into the lung, both *in utero* or at the time of birth, disrupts airflow, increases the risk of pneumothorax, and leads to inflammation and surfactant inactivation. The result is lung atelectasis and ventilation perfusion mismatch leading to respiratory failure as well as predisposition toward persistent pulmonary hypertension of the newborn, a complication that may require extracorporeal membrane oxygenation (ECMO). Three randomized trials evaluated surfactant administration in term infants with respiratory failure from MAS. Both Findlay et al¹² and Lotze et al¹³ reported that surfactant therapy reduces the incidence of respiratory failure requiring ECMO. Short-term oxygenation may also be improved.¹⁴ In a metaanalysis¹⁵ of 208 treated infants, the relative risk of ECMO is reduced by up to one third (RR, 0.64; 95% CI, 0.46 to 0.91). There were no differences in the risk of other pulmonary morbidities, including pneumothorax, chronic lung disease, or mortality. Of note, these studies were conducted prior to the introduction of inhaled nitric oxide; the magnitude of the effect of surfactant on pulmonary morbidity may be altered by the use of inhaled nitric oxide. Although BAL with dilute surfactant in patients with MAS showed promise in lessening the severity of lung injury,¹⁶ concerns regarding the safety of the BAL procedure have prevented wide acceptance of the practice.¹⁷

Other Neonatal Lung Diseases

Respiratory failure in term infants occurs at a developmental stage when the lung surfactant system is nearly mature. Hence, acute lung injury (ALI) leading to respiratory failure in term infants more closely resembles ARDS seen in older children and adults than infant RDS. SRT is effective in improving lung function in term infants with respiratory failure, especially those with sepsis and pneumonia.^{13,18–20} Although surfactant deficiency has been

found in an animal model²¹ of congenital diaphragmatic hernia (CDH), randomized studies of SRT in CDH patients have not been performed. SRT has not been an effective treatment for infants with congenital SP deficiency, especially SP-B deficiency.²²

ARDS

Pediatric Population: Whereas RDS in premature infants results from a quantitative deficiency of surfactant leading to atelectasis and progressive hypoxemia, the mechanisms by which ALI lead to ARDS are more complex. In ARDS, deficient surfactant pools resulting from ALI are further impaired by the inactivation of native surfactant by plasma proteins, inflammatory mediators, and cellular debris. Perhaps due to the complex nature of the lung injury, SRT in pediatric ARDS patients has not shown improvements in lung function similar to those occurring in infants with RDS. However, the results of an RCT²³ of SRT in pediatric patients ages 1 month through 21 years with ALI treated with SRT early in the course of their illness have suggested benefit. Although there was no difference in the primary outcome (ventilator-free days at 28 days after therapy), important differences in secondary outcomes were identified, including a significant reduction in mortality rate (36% vs 19%, respectively; $p = 0.03$) and improvement in oxygenation index at 12 h following SRT. However, the number of days receiving supplemental oxygen, hospital lengths of stay, and hospital charges were not reduced.²³

Adult Population: Three large adult trials of SRT^{24–26} have failed to demonstrate a benefit in adults with ARDS. Whether the failure of SRT to improve outcomes for adults with ARDS is attributable to the nature of lung injury, the timing of therapy, or the delivery and dose of surfactant, the influence of comorbidities that often occur in adult patients with ARDS is unknown. Routine SRT for adult patients with ARDS cannot be recommended based on the current data.

IMPLICATIONS FOR PRACTICE

Methods of Surfactant Administration

SRT requires the placement of an endotracheal tube through which surfactant is directly instilled into the patient's lungs. The dose (1.5 to 4 mL/kg body weight, depending on the preparation) is instilled into the lung in divided aliquots, each of which is administered in a different body position to

help the drug disperse evenly throughout the lung. Although the surfactant is FDA approved for use as single-dose vials, it appears to be stable with repeated cycles of warming and cooling, as may be needed if it is dispensed as a multidose vial. Cost savings when the surfactant is dispensed using a multiuse vial strategy may be substantial.²⁷ Surfactant administration results in a rapid improvement in oxygenation, as atelectatic alveoli and lung segments are inflated and ventilation-perfusion matching improves. Changes in pulmonary function measurements, such as improved compliance and increased functional residual capacity and tidal volume, happen more slowly.²⁸ The improved lung aeration is seen quickly (within 1 h) on chest radiographs as better lung volumes, clearer lung fields, and resolution of air bronchograms. SRT may be administered by a health-care provider who has been trained in its administration and is prepared to treat mild complications of administration such as transient oxygen desaturation, apnea, or bradycardia. These complications usually resolve quickly with manual ventilation. Pulmonary hemorrhage and endotracheal tube obstruction by surfactant are infrequent but more serious complications of administration.

Surfactant Treatment Without Mechanical Ventilation

Surfactant is often administered to patients soon after endotracheal intubation and the initiation of mechanical ventilation. Mechanical ventilation causes ALI due to barotrauma and volutrauma, leading to lung inflammation and worsening RDS. Surfactant administration via transient intubation offers the potential benefits of SRT without a risk of ALI from mechanical ventilation. Among infants with early RDS (those with a fraction of inspired oxygen requirement of < 40%), surfactant administration via transient intubation with rapid extubation to nasal CPAP reduces both the need for mechanical ventilation by up to 40%^{29–31} and the incidence of pneumothorax.³²

Administration Without Intubation

Surfactant administration by endotracheal intubation is the only proven means of adequately delivering surfactant to the lungs of infants, children, or adults with respiratory failure. Attempts to aerosolize, nebulize, or instill surfactant via BAL have been disappointing. Surfactant administration via laryngeal mask airway and via intrapartum hypopharyngeal instillation may have promise as techniques for administering prophylactic surfactant without intubation.^{33,34} Efforts to develop new surfactant prepa-

rations and delivery mechanisms that allow less invasive delivery of surfactant are ongoing.

Billing

Effective January 1, 2003, SRT is bundled into Current Procedural Terminology (CPT) codes for both neonatal intensive care admission day (CPT code 99295) and subsequent day (CPT code 99296) care of infants who are < 31 days of age. For patients who are 31 days of age up to 24 months of age, surfactant administration is bundled into pediatric intensive care codes for admission day (CPT code 99294) and subsequent day care (CPT code 99293). Physician work to administer surfactant is encompassed in these codes; mid-level medical providers such as respiratory therapists, neonatal nurse practitioners, or advanced practice nurses who administer surfactant cannot bill separately. If medical care does not fall into one of these codes, a comprehensive CPT code for surfactant administration does not exist, but could be billed under the components of the administration (*ie*, endotracheal intubation, CPT code 31500; and administration of inhaled medications, CPT code 94664).

Beginning in the spring of 2006, The American Medical Association/Specialty Society Relative Value Scale Update Committee conducted a survey of medical providers to evaluate the physician effort involved in surfactant administration. The survey evaluates provider perception of the physician work involved in procedures with established relative value unit values compared with the effort involved in surfactant administration. Physician effort is evaluated in the following four key domains: mental effort and judgment, technical skill, and physical effort, as well as the psychological stress that occurs when an adverse outcome has serious consequences. A relative value unit value for surfactant administration will be proposed following the conclusion of the survey. A specific CPT code for SRT will be available in spring 2007.

SUMMARY

Advances in prenatal care, neonatal ventilation, and SRT have greatly reduced mortality from RDS among premature infants, especially mildly preterm infants. Prophylactic SRT in patients who are at risk for RDS, particularly those infants born at < 30 weeks gestation, improves neonatal survival and reduces morbidity. For infants in whom RDS develops, SRT early in the course of RDS, before surfactant inactivation plays a prominent role in lung pathophysiology, is superior to later SRT when lung disease is more advanced. Term infants with MAS,

sepsis, or pneumonia benefit from SRT with improved lung function and a reduced need for ECMO. Consistent with the benefits of early treatment, SRT provided early in the respiratory course of pediatric patients with ALI who are otherwise well may reduce mortality, especially for patients in their first year. The use of SRT in other disorders, such as CDH, and in adult populations cannot be recommended based on the available data. The development and testing of newer surfactants, which may be more resistant to inactivation or administered less invasively (without endotracheal intubation) is in progress. For now, effective surfactant administration requires the placement of an endotracheal tube and can be performed by mid-level providers who are experienced in surfactant instillation.

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