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CLINICAL REPORT

Surfactant-Replacement Therapy for Respiratory Distress in the Preterm and Term Neonate

Guidance for the Clinician in Rendering Pediatric Care

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ABSTRACT

Respiratory failure secondary to surfactant deficiency is a major cause of morbidity and mortality in preterm infants. Surfactant therapy substantially reduces mortality and respiratory morbidity for this population. Secondary surfactant deficiency also contributes to acute respiratory morbidity in late-preterm and term neonates with meconium aspiration syndrome, pneumonia/sepsis, and perhaps pulmonary hemorrhage; surfactant replacement may be beneficial for these infants. This statement summarizes indications, administration, formulations, and outcomes for surfactant-replacement therapy. The impact of antenatal steroids and continuous positive airway pressure on outcomes and surfactant use in preterm infants is reviewed. Because respiratory insufficiency may be a component of multiorgan dysfunction, preterm and term infants receiving surfactant-replacement therapy should be managed in facilities with technical and clinical expertise to administer surfactant and provide multisystem support.

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Key Words
surfactant, antenatal steroids, respiratory distress syndrome, meconium aspiration syndrome, neonatal pneumonia, neonatal sepsis, congenital diaphragmatic hernia, pulmonary hemorrhage, persistent pulmonary hypertension, preterm, term

Abbreviations
RR—relative risk
CI—confidence interval
NNT—number needed to treat

BACKGROUND

Surfactant replacement was established as an effective and safe therapy for immaturity-related surfactant deficiency by the early 1990s.[1–21] Systematic reviews of randomized, controlled trials have confirmed that surfactant replacement reduces initial inspired oxygen and ventilation requirements as well as the incidence of respiratory distress syndrome, death, pneumothorax, and pulmonary interstitial emphysema (Table 1).[2–4,13]

After the initial surfactant efficacy and safety trials were conducted, additional studies led to refinements in treatment strategies,[5–7,10,11,13,22–36] choice of preparations,[37–54] techniques for administration,[55–65] and indications other than respiratory distress syndrome.[66–87] The preponderance of evidence indicates that surfactant replacement increases survival rates without an increase in risk of disabilities. Thus, surfactant replacement is associated with an absolute increase in the number of preterm infants who survive with and without disabilities.[88–112] However, the risk of long-term disability remains uncertain, because few follow-up studies at school age and adolescence for preterm infants treated with surfactant have been reported.*

Antenatal steroid use to stimulate structural maturation and surfactant synthesis in the fetal lung increased significantly after completion of the pivotal surfactant trials.[113–127] Investigations powered to assess the benefit of antenatal steroid exposure combined with surfactant replacement have not been reported, although secondary analyses of surfactant trials,[113,114,116] animal studies,[125–127] and clinical experience have indicated that, together, the 2 therapies have an additive effect. Preliminary studies of either continuous positive airway pressure alone or exogenous surfactants and rapid extubation to continuous positive airway pressure have suggested that the need for surfactant replacement and incidence of bronchopulmonary dysplasia in extremely preterm infants may be reduced.[128–144]

The purpose of this clinical report is to update and expand our previous statement about surfactant replacement in newborn infants.[1] Specifically, the topics reviewed include efficacy in preterm infants, prophylactic versus rescue surfactant replacement, surfactant preparations and administration techniques, effects of surfactant on short-term and long-term outcomes, and surfactant replacement for respiratory disorders other than respiratory distress syndrome. The impact of antenatal steroid exposure and continuous positive airway

*Refs 90, 93, 94, 101–103, 106, 107, and 111.

TABLE 1 **Meta-analyses of Surfactant Replacement: Prophylaxis and Rescue Treatment With Animal-Derived and Synthetic Surfactant**

Outcome	Prophylaxis, Typical RR (95% CI)		Rescue, Typical RR (95% CI)	
	Animal Derived[3]	Synthetic[2]	Animal Derived[13]	Synthetic[4]
Incidence and severity of respiratory distress syndrome	Decreased	Inconsistent response	Not available	Decreased
Mortality	0.60 (0.44–0.83)	0.70 (0.58–0.85)	0.67 (0.58–0.76)	0.73 (0.61–0.88)
Pneumothorax	0.35 (0.26–0.49)	0.67 (0.50–0.90)	0.37 (0.25–0.50)	0.64 (0.55–0.76)
Pulmonary interstitial emphysema	0.46 (0.35–0.60)	0.68 (0.50–0.93)	Not available	0.62 (0.54–0.71)
Bronchopulmonary dysplasia or death	0.84 (0.75–0.93)	0.89 (0.77–1.03)	Not available	0.73 (0.65–0.83)

pressure on respiratory distress syndrome and surfactant replacement is also discussed. Implications for the clinical use of surfactant and research considerations are suggested.

PRETERM INFANTS AND SURFACTANT EFFECTIVENESS IN CLINICAL TRIALS

Surfactant trials with preterm infants have included those between 23 and 34 weeks' gestation and/or with birth weights between 500 and 2000 g.† However, the focus of many trials, especially prevention studies, has been on infants of less than 30 weeks' gestation and/or with birth weights of less than 1250 g. The results of subgroup analyses from such studies have indicated that surfactant therapy reduced mortality rates most effectively in infants of less than 30 weeks' gestation or with birth weights of less than 1250 g and more often in male infants.[8,11,15,22,27,96] The incidence of other coexistent morbidities in preterm infants, such as bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, nosocomial infections, retinopathy of prematurity, and patent ductus arteriosus, has not changed with surfactant replacement.[2–5,7,8,22,24] The onset of clinical signs of patent ductus arteriosus may occur earlier,[145–148] and the incidence of pulmonary hemorrhage, especially in infants of less than 27 weeks' gestation, may be increased.[2,19,149] Of note, surfactant replacement reduces the incidence of pneumothorax, pulmonary interstitial emphysema, and the combined outcome of death or bronchopulmonary dysplasia compared with no surfactant replacement (Table 1); these findings suggest that lung injury is reduced after surfactant replacement. Surfactant replacement is also effective for larger and more mature preterm infants with established respiratory distress syndrome.[8,9,22] Compared with controls with similar weights and gestations, larger and more mature surfactant-treated infants had a lower incidence of death (3.4% vs 6.7%; relative risk [RR]: 0.56; 95% confidence interval [CI]: 0.35–0.88; number needed to treat [NNT]: 33)[8,9] and bronchopulmonary dysplasia (5.8% vs 10%; RR: 0.57; 95% CI: 0.40–0.81; NNT: 25) (Appendix).[8,9]

PROPHYLACTIC VERSUS RESCUE SURFACTANT

A prophylactic, or preventive, surfactant strategy is defined as intubation and surfactant administration to infants at high risk of developing respiratory distress syndrome for the primary purpose of giving surfactant rather than treatment of respiratory distress syndrome; this has been operationalized in clinical studies as surfactant administration before the onset of respiratory symptoms or efforts, before initial resuscitation efforts, or, most commonly, after initial resuscitation but within 10 to 30 minutes after birth.‡ This contrasts with a rescue, or treatment, surfactant strategy, in which surfactant is given to preterm infants with established respiratory distress syndrome. Rescue surfactant is most often administered within the first 12 hours after birth when specified threshold criteria for respiratory distress syndrome are met.[9,22–28,34,35] Early rescue was defined as surfactant treatment within 1 to 2 hours of birth, and late rescue was defined as surfactant treatment 2 or more hours after birth.[22–28,34–37]

Preterm infants born at or earlier than 30 weeks' gestation have benefited from both prophylactic and rescue surfactant administration.[5–11,13,14,22,24–28] However, infants receiving prophylactic surfactant have had a lower incidence and severity of respiratory distress compared with those treated after developing respiratory distress syndrome.[5–7,10,11,13,22,24–28] Infants receiving prophylactic surfactant also have encountered fewer complications[5–8,11,13,14,22,25–28] of respiratory distress syndrome, such as death (RR: 0.61; 95% CI: 0.48–0.77; NNT: 22), pneumothorax (RR: 0.62; 95% CI; 0.42–0.89; NNT: 47), pulmonary interstitial emphysema (RR: 0.54; 95% CI: 0.36–0.82; NNT: 40), and the combined outcome of bronchopulmonary dysplasia or death (RR: 0.85; 95% CI: 0.76–0.95; NNT: 24).[26]

The risk of developing bronchopulmonary dysplasia after prophylactic surfactant compared with rescue surfactant has been reported in secondary analyses of clinical trials as no different,[20,26] decreased,[23,25,29] and increased.[13] Small sample sizes in the individual clinical trials were insufficient to evaluate the secondary outcome of bronchopulmonary dysplasia alone.[13,20–29] Therefore, the risk of bronchopulmonary dysplasia in preterm infants of less than 30 weeks' gestation who received prophylactic surfactant compared with those who received later selective treatment is unclear.

The risks of developing other complications of prematurity, such as retinopathy of prematurity, patent

†Refs 5–11, 20, 22–24, 27, 30, 39, 40, and 42.

‡Refs 2–4, 10, 13, 20, 22–25, 27, 28, 30, 39, 40, 42, and 65.

ductus arteriosus, and intraventricular hemorrhage, have been evaluated as secondary outcomes in comparative trials of prophylaxis and rescue surfactant treatment.[2,3,13,20,26] The preponderance of evidence suggests that the incidence of these outcomes is not significantly different.[13,20,26] It is interesting to note, however, that a reduced risk of intraventricular hemorrhage after prophylactic surfactant compared with rescue surfactant was reported in 2 clinical trials and 1 meta-analysis.[30,32,33] The findings in these reports have not been corroborated or explained.

Despite the advantages of a prophylactic surfactant strategy for infants born at less than 30 weeks' gestation, many such infants are treated only after respiratory distress syndrome has become established.[19,31] In a large North American cohort of 47 608 infants of less than 30 weeks' gestation born between 1998 and 2000, 27% received surfactant in the delivery room and 44% received surfactant by 30 minutes of age.[31] Before 6 hours of age, however, 79% had been given surfactant.

Few studies have compared prophylactic surfactant with early rescue treatment and early rescue treatment with late rescue treatment.[34–36,65] Although limited, the results of such studies indicate that surfactant administered prophylactically or as soon as possible in the course of respiratory distress is more effective than late rescue surfactant at improving outcomes.§ It is important to note that such studies were performed with populations of infants who were infrequently exposed to antenatal steroids.[22–25,27–30,35] Thus, the benefits and risks of these different dosing strategies in infants exposed to antenatal steroids have yet to be determined.

ANIMAL-DERIVED VERSUS SYNTHETIC SURFACTANT

Both animal-derived and synthetic surfactants are beneficial for prophylaxis and rescue of respiratory distress syndrome in preterm infants.[2–5,7–11,14,23,24,39,40] Treatment with animal-derived surfactants (beractant, calfactant, poractant) have several advantages over first-generation protein-free synthetic surfactants (eg, colfosceril palmitate, Pumactant [Britannia Pharmaceuticals Ltd, Redhill, Surrey, England], artificial lung-expanding compound).[13,37–40,44–48,58] These advantages include lower mortality rates (RR: 0.86; 95% CI: 0.76–0.98; NNT: 40),[44] lower inspired oxygen and ventilation requirements early in the course of respiratory distress syndrome, and fewer pneumothoraxes (RR: 0.63; 95% CI: 0.53–0.75; NNT: 22).[13,37,38,46,47,58] Of note, first-generation protein-free synthetic surfactants are no longer widely available.

New synthetic surfactants that contain proteins or peptides that mimic surfactant protein activity are under investigation.[39–41,49–51] One such surfactant, lucinactant, contains a peptide that mimics the action of surfactant protein B and has been investigated in human clinical trials.[39–41] Compared with colfosceril palmitate, a first-generation non–peptide-containing synthetic surfactant, lucinactant reduced respiratory morbidity but did not reduce all-cause mortality.[40] When compared with infants receiving the animal-derived surfactants beractant and poractant alfa, infants receiving lucinactant were found to have similar rates of mortality and morbidity from respiratory distress syndrome.[39,40] More analysis is needed before the findings from lucinactant studies can be generalized because of questions about early trial closure and limited statistical power.[39–41] Moreover, the metabolic fate of lucinactant and its component chemicals and potential risks introduced by the requirement to convert the lucinactant gel into liquid by using a special warming cradle immediately before instillation need additional study.[40,41]

Complications of prematurity are not significantly different between preterm infants treated with various animal-derived surfactants and those treated with synthetic surfactants.‖ Such complications include intraventricular hemorrhage, periventricular leukomalacia, pulmonary hemorrhage, sepsis, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, and bronchopulmonary dysplasia.

Animal-derived surfactants in clinical use are modified or purified from bovine or porcine lungs.¶ All commercially available animal-derived surfactants are effective for prevention and treatment of respiratory distress syndrome. However, it is unclear whether significant differences in clinical outcomes exist among the available products.[32,33,39–43,45–48]

Adverse immunologic and infectious complications from exposure to proteins and other components of these animal products have not been identified.[52,53,88,98] Efforts to develop more effective and safer surfactant formulations continue to be warranted because of concerns with animal-derived surfactants for transmission of microbes, exposure to animal proteins and inflammatory mediators, susceptibility to inactivation, and inconsistent content.[39,40,49,51] Newer synthetic surfactant preparations, if proven to be effective and safe, may address these concerns.[39,40,54] Furthermore, the addition of synthetic surfactants to the repertoire of surfactant products provides an animal-free surfactant option.

SURFACTANT ADMINISTRATION

Surfactant-administration strategies have been based on manufacturer guidelines for individual surfactants. Dose, frequency of administration, and treatment procedures have been modeled after research protocols.[7,14,37,39,40,56,57] Furthermore, repeated doses of surfactants given at intervals for predetermined indications have decreased mortality and morbidity compared with placebo or single surfactant doses.[7,8,55,57]

Prophylactic surfactant administration after initial resuscitation and stabilization has been associated with fewer complications and similar outcomes than administration before initiation of resuscitative efforts.[65] On the other hand, when given to rescue infants with established respiratory distress syndrome, administration of surfactant early in the course has resulted in better outcomes than administration later in the course.[34,35] Surfactant-administration procedures may be complicated by transient airway ob-

§Refs 5–7, 10, 11, 13, 20, 22, 24–28, 34, and 35.

‖Refs 37–40, 43, 44, 46–48, 58, and 148.

¶Refs 7, 8, 10, 11, 14, 22, 28, 38, 43, and 46–48.

struction and inadvertent instillation into the right mainstem bronchus or esophagus. Intratracheal delivery of surfactant can also result in rapid improvement in lung volume, functional residual capacity, and compliance. If so, expeditious changes in mechanical ventilator settings should be made to minimize the risks of lung injury and air leak. Clinicians with expertise in these procedures should be responsible for surfactant administration whenever surfactant is given.

Surfactant has been administered through an endotracheal tube located in the trachea of infants either by bolus or infusion through an adaptor port on the proximal end of the endotracheal tube. In an animal model, administration of surfactant as an intratracheal bolus while disconnected from the mechanical ventilator has more uniform distribution than an infusion administered over 30 minutes through a side-hole adapter.[60] However, a small clinical trial of human preterm infants showed no significant differences in clinical outcomes.[61] During administration, oxygen desaturation occurred more often when bolus administration was used, whereas reflux into the endotracheal tube occurred more often when the infusion technique was used. Similar clinical outcomes were also found when surfactant was administered as a bolus or as a 1-minute infusion through a side-hole adapter.[150] Because data are conflicting and limited, the optimal method of surfactant administration in preterm infants has yet to be clearly proven.

There is insufficient evidence to recommend an optimal number of fractional doses of surfactant. There was no difference in clinical outcomes when 2 fractional doses of surfactant were given in 2 body positions compared with 4 fractional doses given in 4 positions.[61] Aerosolized surfactant preparations and continuous positive airway pressure–aided delivery of pharyngeal surfactant theoretically could allow administration without intubation; these preparations and route of delivery have yet to be proven effective.[59,62–64]

SURFACTANT AND PULMONARY OUTCOMES

The incidence of bronchopulmonary dysplasia in very low birth weight infants has not changed with surfactant replacement, although survival without bronchopulmonary dysplasia has increased.[2–5,7,22,24,26] In preterm infants born after 29 weeks' gestation, a significantly lower incidence of bronchopulmonary dysplasia has been reported in 2 trials.[8,9] Despite surfactant treatment, the risk of respiratory abnormalities later in infancy (recurrent wheezing, asthma, respiratory infection, pulmonary-function test abnormalities) and early childhood remains high for preterm infants with respiratory distress syndrome who require mechanical ventilation.[88–99] In a small number of patients followed through school age, pulmonary-function studies seem improved by surfactant replacement.[90] Additional long-term respiratory-function studies are needed of children who have received surfactant as neonates.

SURFACTANT AND NONPULMONARY OUTCOMES

Surfactant replacement increases survival rates without a change in the incidence of neurologic, sensory, or developmental disability in preterm infants followed through infancy# and school age.[101–103] There is limited information about the effects of surfactant replacement on outcomes at adolescence. An association of surfactant-replacement therapy with cerebral palsy, poor cognitive function, and lower teacher rating of school performance was suggested for 126 infants who were born before 29 weeks' gestation and evaluated by structured telephone interview at 12 to 15 years of age.[102] Interpretation of these findings is hampered by small, nonrandomly assigned comparison groups from 3 different protocols; dependence on recall; and bias to include infants with higher severity of illness, because surfactant was given for rescue in 61% of the treated infants. The incidence of neurodevelopmental problems in the surfactant-treated children in this trial was similar to that reported in children born preterm before the introduction of surfactants into clinical medicine.[102,103,107,109,110] Thus, it is difficult to generalize the frequency and severity of nonpulmonary morbidity at adolescence in those who received surfactant therapy as newborn infants.** However, we can conclude that surfactant therapy increases survival without altering the incidence of neurosensory and developmental disabilities.[101,102,107,109–111] As a result, there has been an absolute increase in the number of infants who survive with and without disabilities.

SURFACTANT REPLACEMENT FOR RESPIRATORY DISORDERS OTHER THAN RESPIRATORY DISTRESS SYNDROME

Surfactant activity may be altered in respiratory disorders other than respiratory distress syndrome.[66–87] Surfactant inactivation and secondary dysfunction may occur with conditions such as meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, neonatal pneumonia, and pulmonary hemorrhage. Techniques for surfactant administration, surfactant dosage, patient populations, entry criteria, and study outcomes in the small randomized trials and case series of surfactant replacement in neonates with secondary surfactant deficiency vary considerably.[68,69,72,86,87] Additional studies are needed to establish the value and limitations of surfactant therapy for these conditions.[77,81,86,87]

Meconium aspiration syndrome with severe respiratory failure and persistent pulmonary hypertension may be complicated by surfactant inactivation.[66–70,72–75] Surfactant replacement by bolus or slow infusion in infants with severe meconium aspiration syndrome improved oxygenation and reduced the severity of respiratory failure, air leaks, and need for extracorporeal membrane oxygenation (RR: 0.64; 95% CI: 0.46–0.91; NNT: 6).[67–70,72,75] Although there was no increase in acute morbidity in these infants, transient oxygen desaturation and endotracheal tube obstruction occurred during bolus administration in nearly one third of the surfactant-

#Refs 88, 89, 92, 93, 95, 98, 100–105, and 107–110.

**Refs 88, 89, 92, 93, 95, 98, 100–103, 109, 135, 136, and 140–142.

treated infants.[69] Surfactant lavage for meconium aspiration was evaluated in a small, randomized trial; trends toward lower duration of ventilation and severity of illness were reported.[66,72,78] However, the failure to complete the lavage procedure in 3 of 15 patients warrants additional safety studies.[72,78]

Surfactant replacement for neonates with severe primary persistent pulmonary hypertension of the newborn did not significantly reduce the need for extracorporeal membrane oxygenation in a small clinical trial.[70] However, surfactant improved oxygenation and reduced the need for extracorporeal membrane oxygenation when parenchymal lung disease was present.[66–70,73,77] Surfactant administration to neonates who were receiving extracorporeal membrane oxygenation also reduced the duration of extracorporeal membrane oxygenation.[74]

Surfactant inactivation may be associated with pneumonia.[66,71,76,86,87] A subgroup of infants with sepsis in a small randomized trial of surfactant rescue therapy showed improved oxygenation and reduction of the need for extracorporeal membrane oxygenation.[69] Newborn infants with pneumonia or sepsis receiving rescue surfactant also have demonstrated improved gas exchange compared with infants without surfactant treatment.[66,71,73,76,77] The number of neonates who received surfactant for sepsis and pneumonia in these clinical reports is small.

Surfactant treatment for pulmonary hemorrhage is plausible, because blood inhibits surfactant function.[66,79,80,87] However, only a few retrospective and observational reports have documented the benefits from such therapy, and the magnitude of benefit remains to be established.[79,80,87] Such proof is unlikely to materialize soon, because pulmonary hemorrhage is an unpredictable complication, and randomized trials would be difficult to design and implement.

Congenital diaphragmatic hernia may be associated with surfactant insufficiency. Although measurements of disaturated phosphatidylcholine from lungs of infants with congenital diaphragmatic hernia show synthetic rates similar to those from infants without diaphragmatic hernia, pool sizes and kinetics are altered.[82,83] However, surfactant treatment of a large series of infants with congenital diaphragmatic hernia did not improve outcomes. In fact, use of extracorporeal membrane oxygenation, incidence of chronic lung disease, and mortality actually increased.[66,83–85]

MONITORING MULTIORGAN SYSTEM FUNCTIONS, INTENSIVE CARE, AND SURFACTANT THERAPY

Infants who require surfactant are at high risk of multiorgan dysfunction. For such infants, surfactant replacement is only 1 of the treatments needed. Ideally, such infants would be delivered at institutions that have the necessary services to perform complete neonatal resuscitation and stabilization procedures.[151,152] Such services include having the capability to monitor the status of all major organ systems; having the capability to anticipate, recognize, and treat the initial complications of prematurity or other critical illness; and having surfactant therapy available. It is expected that hospitals with delivery services provide for these capabilities. If delivery would occur at a location without such service (such as in a home, ambulance, emergency department, or medical facility without delivery services), after initial resuscitation and stabilization, such infants are best managed by transport or nursery personnel with technical and clinical expertise to provide comprehensive intensive care services, including surfactant administration.[151,152]

ANTENATAL STEROIDS AND SURFACTANT REPLACEMENT

Surfactant trials that proved efficacy were performed at a time when antenatal steroid therapy was given infrequently.[117,118] By the late 1990s, most mothers of preterm infants delivered at less than 30 weeks' gestation had received antenatal steroids (58%–92%).[18,19,43,79,118,153–155] Antenatal steroids significantly reduce mortality (RR: 0.62; 95% CI: 0.51–0.77; NNT: 23),[115] respiratory distress syndrome (RR: 0.65; 95% CI: 0.47–0.75; NNT: 12),[115] and surfactant use in preterm infants (RR: 0.45; 95% CI: 0.22–0.93; NNT: 9),[115] most consistently in those born between 28 and 34 weeks' gestation.[18,25,113–120,122]

Results of observational studies and clinical trials have inferred that antenatal steroids may reduce the need for prophylactic and early rescue surfactant replacement in infants born after 27 to 28 weeks' gestation,[19,31,35,36] but no randomized, controlled trials have addressed this issue. In infants born at or earlier than 27 weeks' gestation, the incidence of respiratory distress syndrome is not reduced after exposure to antenatal steroids, although the severity of illness seems to be lower.[115,116,118–120]

Infants born before 32 weeks' gestation who received both antenatal steroids and postnatal surfactant were found on subgroup analyses to have significant reductions in mortality, severity of respiratory distress, and air leaks when compared with subgroups who received neither steroids nor surfactant, antenatal steroids only, or surfactant only.[113,114,121] This finding corroborates evidence from animal models of respiratory distress syndrome that the combination of antenatal steroids and postnatal surfactant improves lung function more than either treatment alone.[113,125–127]

Surfactant trials that compared prophylaxis and rescue treatment and large clinical experiences during an era of high antenatal steroid use have shown that 40% to 55% of infants born at 29 to 30 weeks' gestation, 20% to 35% of infants born at 27 to 28 weeks' gestation, and 8% to 10% of infants born at or earlier than 26 weeks' gestation do not receive surfactant replacement. Presumably, these infants do not receive surfactant because they have mild or absent respiratory distress syndrome or their conditions have been successfully managed with continuous positive airway pressure.†† Although some infants who are born at earlier than 30 weeks' gestation and exposed to steroids antenatally do not receive surfactant, it is not known whether morbidity may have been reduced if surfactant had been given prophylactically.[30,32,33]

††Refs 15, 18, 19, 22–24, 28–31, and 128–140.

TABLE 2 **Surfactant-Replacement Therapy for Respiratory Distress in Preterm and Term Neonates: Summary of Science, Class of Evidence, and Evidence Levels of Key References**

Summary of Science	Class of Evidence	Evidence Level							
		1	2	3	4	5	6	7	8
1. Surfactant replacement given as prophylaxis or rescue treatment reduces the incidence and severity of respiratory distress syndrome, air leaks, and mortality in preterm infants with surfactant deficiency.	I	Meta-analysis:[2–4, 13, 20, 25, 34]; RCT:[5–9, 11, 14]	[10, 12]						
1a. Prophylactic surfactant administration to infants of <30 weeks' gestation with a low rate of exposure to antenatal steroids reduces mortality, the frequency and severity of respiratory distress syndrome, air leaks, and the combined outcome of bronchopulmonary dysplasia and death compared with infants who receive placebo or rescue surfactant.	I	Meta-analysis:[2, 3, 13, 26]; RCT:[5–7, 10]							
1b. Early rescue surfactant (<2 hours from birth) given to infants of <30 weeks' gestation with a low rate of exposure to antenatal steroids reduces the frequency of adverse respiratory outcomes compared with later rescue surfactant.	I	Meta-analysis:[34]; RCT:[35]							
2. Both animal-derived and synthetic surfactants improve respiratory morbidity and mortality rates in preterm infants with surfactant deficiency.	I	Meta-analysis:[2–4, 13]; RCT:[5, 7–12, 14, 16]							
3. New synthetic surfactants with surfactant protein-like activity are promising new treatments for surfactant-deficiency disorders.	IIa		RCT:[39, 40]						
4. The various surfactant doses, dosing volumes, interdose intervals, and techniques for administering exogenous surfactant used in protocols for clinical trials have improved clinical outcomes.	I	RCT:[7, 8, 14, 37, 39–40, 56–57, 61]					60		
5. The incidence of bronchopulmonary dysplasia in infants of <30 weeks' gestation who have received surfactant is not changed when compared with controls; however, the incidence is lower in treated infants born at ≥30 weeks' gestation.	IIa	Meta-analysis:[3]	8, 9						
6. Surfactant replacement has not been shown to affect the incidence of neurologic, developmental, behavioral, medical, or educational outcomes in preterm infants. The net result is an absolute but proportionate increase in the number of infants with and without disabilities.	IIa	Meta-analysis:[110]	92–95, 97–100		109	91, 96, 111			
7. Surfactant treatment improves oxygenation and reduces the need for extracorporeal membrane oxygenation without an increase in morbidity in neonates with meconium aspiration syndrome and sepsis/pneumonia. Surfactant treatment may also reduce morbidity and mortality for infants with pulmonary hemorrhage.	IIb	Meta-analysis:[67, 77]	68, 69			70–73, 76, 75–80, 86, 87		77	
8. Preterm infants at risk of surfactant deficiency benefit from antenatal steroid exposure.									
8a. Antenatal steroids decrease mortality, the severity of respiratory distress syndrome, surfactant use, and intraventricular hemorrhage in infants of <34 weeks' gestation and decrease the incidence of respiratory distress syndrome in infants of between 28 and 34 weeks' gestation.	I	Meta-analysis:[115]	114, 116, 119, 120, 122			18		113, 114, 117	
8b. Antenatal steroids and postnatal surfactant replacement independently and additively reduce mortality, the severity of respiratory distress syndrome, and air leaks in preterm infants.	IIa	116	117			118		19, 113, 121	
8c. Antenatal steroids may reduce the need for prophylactic and early rescue surfactant replacement in infants born after 27–28 weeks' gestation, although this has not been proven in large RCTs.	IIa		35, 36					19, 31	
9. Continuous positive airway pressure, with or without exogenous surfactant, may reduce the need for additional surfactant and incidence of bronchopulmonary dysplasia without increased morbidity, although this has not been proven in large RCTs.	IIb	RCT:[140] (failed to support hypothesis)	130–132, 138		134, 135	133, 136, 137			

RCT indicates randomized, controlled trial.

Modified from "Levels of Evidence" and "Class of Recommendation" (American Heart Association. *International Liaison Committee on Resuscitation Worksheet Templates*).[152]

An important additional benefit of antenatal steroids is a reduction in risk of intraventricular hemorrhage (RR: 0.60; 95% CI: 0.43–0.83; NNT: 10),[115] an advantage not found with surfactant replacement alone.[114–118,121,122] Antenatal steroids provide no consistent benefit for other complications such as necrotizing enterocolitis, patent ductus arteriosus, infection, or, of particular significance, bronchopulmonary dysplasia in preterm infants born at less than 30 weeks' gestation.[113–116]

CONTINUOUS POSITIVE AIRWAY PRESSURE AND SURFACTANT

Improvements in surfactant formulations and other intervention strategies to minimize the risk of bronchopul-

TABLE 3 **Definitions of Levels of Evidence**

Level of Evidence	Definitions
1	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
2	Randomized clinical trials with smaller or less significant treatment effects
3	Prospective, controlled, nonrandomized, cohort studies
4	Historic, nonrandomized, cohort or case-control studies
5	Case series: patients compiled in serial fashion, lacking a control group
6	Animal studies or mechanical model studies
7	Extrapolations from existing data collected for other purposes, theoretic analyses
8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

monary dysplasia may improve neurologic, behavioral, pulmonary, and developmental outcomes in preterm infants.‡‡ Because initiation of mechanical ventilation is a major risk factor for chronic lung disease in observational studies, some experts have raised concern about intubation and using positive pressure in infants for the sole purpose of administering surfactant.[143,144] Likewise, preliminary success with a strategy of early continuous positive airway pressure with or without rescue surfactant administration in observational, historical control, and small randomized trials has influenced some clinicians to substitute an early rescue strategy for a surfactant prophylaxis strategy for infants of less than 30 weeks' gestation.[19,31,128–142]

In preterm infants of more than 27 weeks' gestation, observational studies have suggested that early continuous positive airway pressure to prevent or treat respiratory distress syndrome without mechanical ventilation may reduce the incidence of bronchopulmonary dysplasia.[136,143,144] In contrast, a multicenter, randomized, controlled trial that compared prophylactic to rescue continuous positive airway pressure revealed no difference in surfactant use, mechanical ventilation, bronchopulmonary dysplasia, air leaks, or other complications of preterm birth.[140]

In preterm infants of less than 28 weeks' gestation or with birth weights of less than 1000 g, the need for mechanical ventilation has been reported to range between 40% and 90% in uncontrolled studies of continuous positive airway pressure.[133,134,137,141] In large cohorts of extremely preterm infants, 80% received mechanical ventilation and 70% received exogenous surfactant.[19,31] A small trial of 104 infants who were born at or earlier than 27 weeks' gestation and randomly assigned to stabilization with or without continuous end-distending pressure in the delivery room revealed that nearly 80% of these infants received mechanical ventilation, mostly because of respiratory distress within the first hours after birth.[138] The rates of surfactant administration and complications associated with extreme prematurity were not reported. Thus, until results from large randomized trials are reported, it is unclear whether the use of early end-distending pressure will safely reduce the need for surfactant administration and incidence of complications of extreme prematurity (eg, bronchopulmonary dysplasia).

Surfactant administration, coupled with continuous positive airway pressure, for preterm infants with respiratory distress syndrome has been evaluated in small, randomized trials.[130–132,142] In these trials, infants were randomly assigned to groups for surfactant versus control,[130] early versus late surfactant,[131] or surfactant followed by continuous positive airway pressure versus surfactant and mechanical ventilation.[132] Continuous

‡‡Refs 29, 34, 79, 91, 96, 100–106, and 140.

TABLE 4 **Definitions of Class and Required Level of Evidence**

Class	Clinical Definition	Required Level of Evidence
I. Definitely recommended; definitive, excellent evidence provides support	Always acceptable, safe Definitely useful Proven in both efficacy and effectiveness Must be used in the intended manner for proper clinical indications	One or more level 1 studies are present (with rare exceptions) Study results consistently positive and compelling
II. Acceptable and useful	Safe, acceptable Clinically useful Not yet confirmed definitively	Most evidence is positive Level 1 studies are absent, inconsistent, or lack power No evidence of harm
IIa. Acceptable and useful with good evidence	Safe, acceptable Clinically useful Considered to be treatments of choice	Generally higher levels of evidence Results are consistently positive
IIb. Acceptable and useful with fair evidence	Safe, acceptable Clinically useful Considered to be optional or alternative treatments	Generally lower or intermediate levels of evidence Generally, but not consistently, positive results
III. Not acceptable, not useful, may be harmful	Unacceptable Not useful clinically May be harmful	No positive high-level data Some studies suggest or confirm harm
Indeterminate	Research just getting started Continuing area of research No recommendations until further research	Minimal evidence is available Higher studies in progress Results inconsistent, contradictory Results not compelling

positive airway pressure plus surfactant was associated with a reduction in mechanical ventilation compared with the control groups. This suggested that continuous positive airway pressure, combined with surfactant after a brief intubation early in the course of respiratory distress syndrome, had short-term benefit. However, these studies were not powered to assess mortality, the frequency of complications of preterm birth, duration of hospital stay, or the combined outcome of bronchopulmonary dysplasia or mortality.

SUMMARY OF SCIENCE

See Tables 2–4 for class and level of evidence.

1. Surfactant replacement, given as prophylaxis or rescue treatment, reduces the incidence and severity of respiratory distress syndrome, air leaks, and mortality in preterm infants with surfactant deficiency.
   a. Prophylactic surfactant administration to infants of less than 30 weeks' gestation with a low rate of exposure to antenatal steroids reduces mortality, the frequency and severity of respiratory distress syndrome, air leaks, and the combined outcome of bronchopulmonary dysplasia and death compared with infants who receive placebo or rescue surfactant.
   b. Early rescue surfactant (<2 hours from birth) given to infants of less than 30 weeks' gestation with a low rate of exposure to antenatal steroids reduces the frequency of adverse respiratory outcomes compared with later rescue surfactant.
2. Both animal-derived and synthetic surfactants decrease respiratory morbidity and mortality in preterm infants with surfactant deficiency.
3. New synthetic surfactants with surfactant protein–like activity are promising new treatments for surfactant-deficiency disorders.
4. The various surfactant doses, dosing volumes, interdose intervals, and techniques for administering exogenous surfactant used in protocols for clinical trials have improved clinical outcomes.
5. The incidence of bronchopulmonary dysplasia in infants who are born less than 30 weeks' gestation and have received surfactant is not changed when compared with controls; however, the incidence is lower in treated infants born at or later than 30 weeks' gestation compared with untreated infants of the same gestational age.
6. Surfactant replacement has not been shown to affect the incidence of neurologic, developmental, behavioral, medical, or educational outcomes in preterm infants.
7. Surfactant treatment improves oxygenation and reduces the need for extracorporeal membrane oxygenation without an increase in morbidity in neonates with meconium aspiration syndrome and sepsis/pneumonia. Surfactant treatment may also reduce morbidity and mortality for infants with pulmonary hemorrhage.
8. Preterm infants at risk of surfactant deficiency benefit from antenatal steroid exposure.
   a. Antenatal steroids decrease mortality, the severity of respiratory distress syndrome, surfactant use, and intraventricular hemorrhage in infants born at less than 34 weeks' gestation and decrease the incidence of respiratory distress syndrome in infants born at between 28 and 34 weeks' gestation.
   b. Antenatal steroids and postnatal surfactant replacement independently and additively reduce mortality, the severity of respiratory distress syndrome, and air leaks in preterm infants.
   c. Antenatal steroids may reduce the need for prophylactic and early rescue surfactant replacement in infants born after 27 to 28 weeks' gestation, although this has not been proven in large, randomized clinical trials.
9. Continuous positive airway pressure, with or without exogenous surfactant, may reduce the need for additional surfactant and incidence of bronchopulmonary dysplasia without increased morbidity, although this has not been proven in large, randomized clinical trials.

CLINICAL IMPLICATIONS

1. Surfactant should be given to infants with respiratory distress syndrome as soon as possible after intubation irrespective of exposure to antenatal steroids or gestational age.
2. Prophylactic surfactant replacement should be considered for extremely preterm infants at high risk of respiratory distress syndrome, especially infants who have not been exposed to antenatal steroids.
3. Rescue surfactant may be considered for infants with hypoxic respiratory failure attributable to secondary surfactant deficiency (eg, meconium aspiration syndrome, sepsis/pneumonia, and pulmonary hemorrhage).
4. Preterm and term neonates who are receiving surfactant should be managed by nursery and transport personnel with the technical and clinical expertise to administer surfactant safely and deal with multisystem illness.

RESEARCH IMPLICATIONS

1. Randomized trials of continuous positive airway pressure, with or without surfactant, during a brief intubation compared with prophylactic or early surfactant replacement in preterm infants are needed.
2. Improved surfactant preparations, surfactant-dosing strategies for infants born to mothers who are receiving antenatal steroids, and noninvasive techniques for surfactant administration need additional study.

3. Surfactant replacement for illnesses other than respiratory distress syndrome needs additional study.
4. It is no longer necessary to include first-generation synthetic surfactants in future studies.

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APPENDIX Death and Bronchopulmonary Dysplasia in Larger Preterm Infants

	Surfactant	Control
Death		
Liechty et al,[8] *n/N*	1/110	6/112
Long et al,[9] *n/N*	26/614	42/623
Total, *n/N* (%)	27/724 (3.4)	49/735 (6.7)
RR (95% CI)	0.56 (0.35–0.88)	
Risk difference	0.03	
NNT	33	
RR reduction	0.44	
Test for heterogeneity		
χ^2	1.38	
df	1	
P	.24	
I^2, %	27.8	
Bronchopulmonary dysplasia		
Liechty et al,[8] *n/N*	24/104	35/98
Long et al,[9] *n/N*	16/614	37/623
Total, *n/N* (%)	42/718 (5.8)	72/721 (10.0)
RR (95% CI)	0.57 (0.40–0.81)	
Risk difference	0.04	
NNT	25	
RR reduction	0.43	
Test for heterogeneity		
χ^2	0.57	
df	1	
P	.45	
I^2, %	0	

Tables were generated by using RevMan 4.2 software (available from the Cochrane Review Web site[156]).

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