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Abstract

Exogenous surfactant is one of only a handful of neonatal therapies that has a strong evidence base, the product of countless basic and clinical studies over roughly 30 years between the first report of respiratory distress syndrome (RDS) as surfactant deficiency and the Food and Drug Administration (FDA) approval of the first surfactant preparation. Why then has surfactant therapy *not* succeeded in other neonatal, pediatric, or adult diseases associated with deficient or dysfunctional surfactant? By reflecting on the successes of surfactant therapy for RDS and examining critically the current evidence base for surfactant therapy in other neonatal pulmonary diseases, the authors chart a course for the future of surfactant therapy in neonatology.

Objectives

After completing this article, readers should be able to:

1. Describe the evidence base for the use of exogenous surfactant for the treatment of RDS.
2. Discuss the justification for considering exogenous surfactant therapy in other pulmonary diseases of the neonate and infant, based on the surfactant pathophysiology of these diseases.
3. Discuss the limitations in the evidence base for exogenous surfactant therapy in other pulmonary diseases of the neonate and infant.
4. Identify needs for future clinical trials, and important considerations in their design, of exogenous surfactant therapy for other pulmonary diseases of the neonate and infant.

Educational Gaps

1. Limited comprehension of the pathophysiology of surfactant in diseases of the neonate and infant, such as RDS, meconium aspiration, congenital diaphragmatic hernia (CDH), bronchiolitis, and bronchopulmonary dysplasia (BPD).
2. Limited understanding of the evidence base for surfactant use in RDS, meconium aspiration, CDH, bronchiolitis, and BPD.
3. Paucity of clinical trials demonstrating efficacy of surfactant treatment in meconium aspiration, CDH, bronchiolitis, and BPD, and need for such trials to advance surfactant therapy.

Abbreviations

BPD:	bronchopulmonary dysplasia
CDH:	congenital diaphragmatic hernia
CPAP:	continuous positive airway pressure
ECMO:	extracorporeal membrane oxygenation
FDA:	Food and Drug Administration
RDS:	respiratory distress syndrome
RSV:	respiratory syncytial virus
SP:	surfactant protein

Introduction

Since the FDA release of surfactant to treat RDS in 1989 (1), there has been a deeper understanding of surfactant physiology (reviewed in Jobe (2)), as well as completion of multiple clinical studies to further delineate and refine the use of exogenous surfactant in RDS. Beyond the established evidence that surfactant administration reduces pneumothorax, pulmonary interstitial emphysema and the combined outcome of BPD or death in preterm infants with surfactant deficiency (3)(4)(5), there is a great deal of work still being

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done. Areas of active investigation include studies of comparative or newer surfactant preparations, timing of surfactant administration (prophylactic versus early treatment versus late treatment), combined treatment modalities (surfactant use +/− continuous positive airway pressure [CPAP]), and the use of surfactant for diseases other than RDS.

Therefore, what is important for clinicians to know in this postsurfactant era? First, clinical implementation of surfactant use needs to make sense based on what has been learned from RDS, and needs to be consistently applied in accordance with the strong evidence base for surfactant therapy. Also, to ensure that patients consistently receive the benefit of decades of basic and clinical research, it is crucial to identify and integrate new information regarding therapeutic uses of surfactant.

Surfactant Fundamentals

In the 30 years that passed between the association of pulmonary surfactant with RDS and the approval of the first exogenous surfactant by the FDA, we learned a considerable amount about how the biochemistry and biophysical properties of surfactant are suited to the disease process of RDS. Although more thoroughly reviewed elsewhere (2), it is important to reflect on the lessons of the presurfactant era specifically related to the etiology of RDS, the associated abnormalities of surfactant biochemistry, and the elements of treatment that are critical to efficacy to begin to understand potential expanded uses for surfactant in other neonatal diseases.

Understanding the Disease

Surfactant is a complex mixture consisting of phospholipids, neutral lipids, and proteins that work together at the air-liquid interface to reduce surface tension in the alveolar space. It became clear that prematurely born infants with RDS exemplified a developmental surfactant deficiency in which all of the components that directly contribute to lowering surface tension—namely phospholipids and the hydrophobic surfactant proteins SP-B and SP-C—were reduced or absent due to immaturity of the alveolar type 2 cell. (6)(7)(8) Studies demonstrating the efficiency of the recycling pathway, in which alveolar surfactant components are taken up by the cell and repackaged into lamellar bodies for re-secretion (reviewed in Jobe and Ikegami (9)), clarified how a single dose of exogenous surfactant could result in sustained effects in both animal models and patients with RDS. The most effective exogenous surfactant preparations for RDS were those that reconstituted that which was missing (saturated phospholipids supplemented with either chemical substitutes or naturally derived surfactant proteins) in a formulation in which they were immediately biophysically active and could be reutilized by the immature type 2 cell until de novo synthetic capacity improved. In addition, the use of antenatal glucocorticoids to enhance de novo synthesis and secretion of surfactant by inducing the expression of surfactant proteins and enzymes of phospholipid biosynthesis in the fetal lung reduced the need for exogenous surfactant therapy. (10) Together, the activity and bioavailability of exogenous surfactant, the ability of the fetal lung to recycle exogenous surfactant, and the enhancement of lung maturity including surfactant production either in response to exogenous glucocorticoids or to the stress of preterm delivery account for the success of surfactant therapy in uncomplicated RDS. Lung injury—either antenatally from infection inflammation or postnatally as a consequence of clinical management—is a primary factor responsible for surfactant treatment failure.

Understanding Surfactant Biochemistry

Initial studies in which dipalmitoyl phosphatidylcholine alone was used to treat RDS in prematurely born lambs failed due to the absence of the hydrophobic surfactant proteins that integrate with the phospholipids and assist in the adsorption of phospholipid to the air-liquid interface. (11) The development of alternate additives to replace the adsorptive roles of SP-B and –C, specifically tyloxapol and hexadecanol, advanced the development of the first FDA-approved surfactant for RDS.

FIRST-GENERATION SURFACTANT: PROTEIN-FREE SYNTHETICS: The first generation of synthetic surfactants contained the crucial phospholipid dipalmitoyl phosphatidylcholine but did not include the surfactant proteins SP-B and SP-C. The most commonly used preparation, Colfosceril Palmitate (Exosurf), improved gas exchange and allowed for weaning of ventilator support in preterm infants with RDS. Additionally, Exosurf resulted in other desirable outcomes: decreased air leak, patent ductus arteriosus, intraventricular hemorrhage, BPD, death, and the combined outcome of BPD/death. (12)(13)(14)(15) Meta-analyses of early studies also revealed no differences in neurodevelopmental outcomes of treated versus nontreated infants. (4)(5)

SECOND-GENERATION SURFACTANTS: ANIMAL-DERIVED SURFACTANTS: Surfactants developed after Exosurf are the group in widespread clinical use today—Survanta, Curosurf, and Infasurf (see Table). They are derived from extracts of minced porcine or bovine lung,

Table. Surfactant Preparations

Surfactant	Synthetic or Natural	Protein-Containing?	Suggested Dose	Comments
Colfosceril Palmitate (Exosurf)	Synthetic	No	5 mL/kg; delivers 67 mg/kg DPPC	DPPC and PG
Beractant (Survanta)	Natural (minced bovine lung extract)	Yes, <1 mg/mL total protein: unspecified SP-B, SP-C (203 mcg/mL)	4 mL/kg; delivers 100 mg/kg phospholipid	Has additional DPPC, tripalmitin and palmitic acid
Poractant Alpha (Curosurf)	Natural (minced porcine lung extract)	Yes, total 1% hydrophobic proteins; 0.3–0.45 mg/mL SP-B; 5.0–11.6 mcg SP-C/microM PL	2.5 mL/kg initial dose; 1.25 mL/kg subsequent dose(s); delivers 100–200 mg/kg phospholipid	Contains only polar lipids; highest concentration of lipids of commercial surfactants
Calfactant (Infasurf)	Natural (bovine lung lavage extract)	Yes: guaranteed 0.26 mg/mL SP-B; 1.26% of PL	3 mL/kg; delivers 105 mg/kg phospholipid	No supplemental lipids added
Lusupultide (Venticute)	Synthetic	Yes, recombinant SP-C only; 2%	No trials in neonates; 50 mg/mL phospholipid	DPPC/POPG in a 7:3 ratio
Lucinactant (Surfaxin)	Synthetic	Yes, 21 amino acid SP-B mimetic peptide; 2.7%	5.8 mL/kg; delivers 174 mg/kg phospholipid	DPPC/POPG in a 3:1 ratio

DPPC=dipalmitoyl phosphatidylcholine; PG=phosphatidylglycerol; POPG=1-palmitoyl-2-oleoylglycero-3-phosphoglycerol; SP-B=surfactant protein B; SP-C=surfactant protein C.

or from lung lavage. Lavage preparations were designed as an alternative to minced extracts due to the potential for less contamination with unwanted lipids and proteins from residual tissue or plasma components. (16) These surfactants include not only phospholipids but have the advantage of containing SP-B and SP-C albeit in variable amounts (Table). Although surfactant phospholipids lower alveolar surface tension, the protein components are essential for in vivo efficacy, as they allow for rapid adsorption and spreading of the surfactant film across the alveolar surface. Comparisons of first- versus second-generation surfactants have demonstrated that while both are effective in treatment of RDS, second-generation surfactants result in lower oxygen requirements and ventilator support in the first 72 hours after administration, fewer pneumothoraces, and a trend towards less BPD/death. (4)(17)

NEWER SURFACTANTS: ENGINEERED PROTEIN COMPONENTS: More recently, a yet third generation of surfactants has emerged containing synthetic proteins designed to mimic the structure and actions of SP-C or SP-B. The presumed advantages of such products are twofold: lot-by-lot consistency in the amounts of these proteins, plus reduction in the theoretical risks related to possible animal-to-human transmission of prion-related infections. The two main engineered surfactants that have been studied in humans are Venticute (r-SP-C-surfactant) and Surfaxin (lucinactant). Venticute (lusupultide) contains recombinant SP-C. Venticute has not been studied in neonates and has only undergone trials in adults with acute lung injury in which short-term physiologic benefits were not accompanied by improvements in survival. (18) By comparison, Surfaxin contains KL_4, a synthetic 21-amino acid peptide consisting of successive repeats of one leucine and four lysines designed to mimic the properties of SP-B. In the two published randomized trials to date, Surfaxin has been shown to be safe and effective and to reduce mortality associated with RDS. (19)(20) However, combined analysis of these studies does not support superiority of Surfaxin over the animal-derived synthetic surfactants currently in widespread clinical use, (17)(21) and at present, RDS is the only FDA-approved use for exogenous surfactant.

Critical Elements for Future Therapeutic Trial Design

Much has been determined about surfactant dosing from animal studies, therapeutic trials, and from subsequent studies of the metabolism of exogenous surfactant through the use of heavy isotope tracing. Some of these basic principles have been described in detail elsewhere (22), and include:

- Surfactant is most effective if delivered before the onset of lung injury, and more may be necessary in the face of lung injury. Direct effects of lung injury on alveolar surfactant include inactivation of surfactant function by environmental exposure (oxidants), degradation (lipases), conversion to inactive structural forms, or inhibition of function (plasma proteins, plasma lipids, and inflammatory products). Indirect effects arising from lung injury include the effects of circulating cytokines that can influence the ability of the alveolar type 2 cell to synthesize new surfactant constituents.
- Homogeneous distribution of surfactant over the large surface area of the lung is critical to the success of therapy. Animal studies have demonstrated the effectiveness of as little as 4 mg/kg of surfactant phospholipid in an uninjured lung. (23) Key elements to be considered in optimizing surfactant distribution include volume of dose (larger is better), rate of administration (faster is better), ventilator assistance (to facilitate airway clearance and alveolar patency), presence of lung liquid (to improve distribution), and positional maneuvers (to combat the effects of gravity).

Evidence for Use of Exogenous Surfactant in Neonatal Lung Diseases Other Than RDS

Meconium Aspiration

DISEASE PATHOGENESIS/ETIOLOGY: In vitro and animal studies have suggested that meconium inactivates components of surfactant, thereby reducing the effectiveness of endogenous surfactant. (24)(25) In addition, airway obstruction, inflammation, protein leak, and retained fetal lung fluid all contribute to the pathogenesis of meconium aspiration syndrome. Furthermore, the need for mechanical ventilation often exacerbates lung injury in meconium aspiration syndrome. Patients with meconium aspiration syndrome demonstrated reduced surfactant phospholipid synthesis and decreased alveolar phosphatidylcholine concentrations in clinical studies utilizing heavy isotope labeling but had normal surfactant half-life and pool size. (26)

CLINICAL TRIALS TO DATE: A recent meta-analysis incorporated four clinical trials (27)(28)(29)(30) of surfactant for meconium aspiration syndrome with a total of 326 patients. (31) Entry criteria included patients who were between <6 hours and <120 hours old at the time of enrollment, with respiratory disease classified as moderate to severe. Surfactant administration had no effect on the primary outcome of mortality assessed in all four trials. The only secondary outcome for which surfactant administration proved to be of benefit was a reduced need for extracorporeal membrane oxygenation (ECMO). These results have been borne out by a more recent small clinical trial using large volume, dilute surfactant as a lavage agent. (32)

CONCLUSION: The potential advantages to providing exogenous surfactant therapy include restoration of alveolar surfactant with the potential for improved distribution owing to retained fetal lung fluid and alveolar edema fluid as discussed above. However, the clinical trials to date only demonstrate a reduction in the need for ECMO. Although all of the trials used second-generation surfactants, there are important issues in study design that may have contributed to the limited success. First, enrollment was restricted to infants with moderate to severe disease, raising concern that postnatal management between delivery and enrollment may have contributed to increased lung injury known to compromise the effectiveness of surfactant therapy. This may explain reports of improved short-term physiologic parameters such as oxygenation index that do not translate into reduced duration of ventilation or hospitalization. With this in mind, the potential benefit of reducing the need for ECMO, especially in areas where this technology is not readily available, is advantageous. In such instances, surfactant therapy should be considered as early as possible to minimize lung injury associated with treatment of meconium aspiration.

Congenital Diaphragmatic Hernia

DISEASE PATHOGENESIS/ETIOLOGY: As CDH is characterized by pulmonary hypoplasia, poor lung compliance and likely altered numbers of alveolar type 1 and 2 epithelial cells, (33)(34) exogenous surfactant as adjuvant treatment for the severe respiratory distress associated with this disease is an attractive concept (reviewed in Benjamin et al. (35)). However, in vitro and animal evidence for a true primary surfactant deficiency in CDH is mixed, with possible phospholipid dysfunction, (36) but normal surfactant protein mRNA levels in lung tissue. (37) Fetal lamb models of CDH have demonstrated lavage samples with low total phospholipid content and clinical improvement with surfactant treatment. (38)(39) Human studies are similarly conflicting. Decreased disaturated phosphatidylcholine and surfactant protein A (SP-A) concentrations have been previously reported by some, (40) whereas stable isotope labeling studies in patients (41) and a recent human autopsy study of infants with CDH (42) demonstrated normal phospholipid pools or surfactant protein concentrations, sug-

gesting that patients with CDH are not surfactant deficient per se.

CLINICAL TRIALS TO DATE: There have been no multicenter randomized trials of surfactant for respiratory failure due to CDH. The few published prospective studies of surfactant for infants with CDH do not demonstrate a clear benefit with surfactant treatment. (43)(44) Most studies reported are case series or chart reviews where surfactant was given prophylactically or as a rescue therapy (45)(46)(47) and outcome differences attributable to surfactant were generally not reported. (48) In two retrospective analyses of patients in the CDH Study Group, surfactant treatment did not improve outcomes, (49) and was associated with increased ECMO use, a higher incidence of chronic lung disease, and lower survival. (50)

CONCLUSION: Although characterized by tissue hypoplasia, it is likely more accurate to think of the CDH lung as *maldeveloped*, rather than *immature*. The severe respiratory compromise associated with CDH is exacerbated by left ventricular and pulmonary arterial hypoplasia, arterial intimal remodeling, and pulmonary hypertension, as well as altered alveolar epithelial cell populations. This more complex description of CDH pathophysiology and the variable timing of surfactant administration postnatally may help to explain why surfactant replacement has not shown a consistent benefit to date. However, this is not to suggest that exogenous surfactant could not have a role in the management of patients with CDH in the future, particularly with regards to addressing the poor lung compliance associated with this disease and surfactant inactivation that can occur with capillary leak and high volume ventilation. Future studies should address the timing, dosing, and clinical scenarios in which a subset of patients with CDH may benefit from exogenous surfactant. However, at this time, routine use of surfactant for patients with CDH cannot be recommended as a standard practice.

Bronchopulmonary Dysplasia

DISEASE PATHOGENESIS/ETIOLOGY: BPD describes the end product of a multitude of injuries and exposures to the preterm lung occurring prenatally, perinatally, and postnatally. It is clear that one component of this complex disease is alveolar epithelial cell injury and dysfunction. Alveolar type 2 cell hyperplasia is a frequent finding in BPD lungs, but there is good evidence that these cells do not function normally. Analysis of surfactant isolated from tracheal aspirate samples of ventilator dependent infants demonstrated high surface tension that correlated inversely with SP-B and –C composition, especially during episodes of clinical deterioration. (51) Explanted lung tissue from patients with BPD undergoing lung transplantation exhibited altered SP-B processing kinetics. (52) Heavy isotope labeling studies of intubated infants with BPD have demonstrated altered surfactant phospholipid pools and reduced recycling of alveolar surfactant phospholipids. (53)(54)

CLINICAL TRIALS TO DATE: There have been no clinical trials of surfactant therapy for established BPD or evolving chronic lung disease. A safety study of surfactant for preterm infants at 7 to 10 days of age who were intubated and at risk for surfactant dysfunction (based on Merrill et al. (51)) was completed recently. (55) Treated patients demonstrated short-term physiologic improvements in surfactant function and in respiratory severity score.

CONCLUSION: It is too simplistic to think that surfactant therapy alone would be successful in the treatment of BPD. However, it is reasonable to think that surfactant therapy may be beneficial as a supportive strategy for infants requiring prolonged mechanical ventilation who are exposed to hyperoxia and volutrauma, and who are at risk for hospital-acquired infections and ventilator-associated pneumonia that can contribute to alveolar epithelial injury and ultimately contribute to BPD. Multicenter, randomized trials will be important to determine whether late, postnatal surfactant therapy will be useful in the management of infants at risk for BPD.

Bronchiolitis

DISEASE PATHOGENESIS/ETIOLOGY: In prematurely born infants, the risk of morbidity and mortality from respiratory syncytial virus (RSV) is disproportionately high, contributing to the 8% to 21% of infants with pre-existing conditions needing mechanical ventilation due to respiratory failure from RSV (recently reviewed in Barreira et al. (56)). RSV binds to Toll-like receptors on epithelial cells lining the upper and lower airways and initiates a brisk inflammatory response that contributes to epithelial cell injury and reduced surfactant production. Collectively, epithelial cell dysfunction, inflammatory cytokines, and epithelial barrier injury leading to alveolar edema are likely to contribute to surfactant abnormalities and respiratory failure in infants with bronchiolitis.

The innate immune system is a primary defense to RSV through binding and inactivation of the virus. The

two *hydrophilic* surfactant proteins, SP-A and SP-D, have lectin binding domains that contribute to the innate defenses through pattern recognition of sugars on the surfaces of bacteria and viruses. Animal studies have demonstrated that absence of SP-A or SP-D results in reduced clearance of RSV from the lung and is associated with worse inflammation, both of which were reversed by providing exogenous SP-A or SP-D. (57)(58) Prematurely born infants have reduced concentrations of SP-A. (59)(60)(61) Similar information is lacking on SP-D in preterm infants, but studies of prematurely born baboons suggest that alveolar concentrations of SP-D may also be reduced compared with term animals and adults. (62) Thus it is reasonable to suggest that deficient SP-A and –D render prematurely born infants more susceptible to infection from RSV and other microorganisms (influenza, ureaplasma, Group B Streptococcus, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Pneumocystis jirovecii*) that are bound by the hydrophilic surfactant associated proteins.

CLINICAL TRIALS TO DATE: To date, three clinical trials involving a total of 79 patients examined the effectiveness of exogenous surfactant therapy for RSV bronchiolitis. (63)(64)(65) All three demonstrated improved respiratory physiology after treatment, and two demonstrated reduction in duration of mechanical ventilation, length of hospitalization (either intensive care unit stay or total hospital days), but all suffer from small numbers. A large clinical trial of surfactant for pediatric acute lung injury involving 159 patients included 33 with RSV or viral, non-RSV bronchiolitis. (66) It is unclear whether bronchiolitis was the only diagnosis in the subgroup analysis on infants <12 months of age for which there was reduced mortality in the surfactant-treated patients.

CONCLUSION: Although promising, the evidence base supporting the widespread use of surfactant for bronchiolitis is insufficient at this time and additional randomized controlled trials are warranted. Especially important for future trials is the inclusion of former preterm infants due to their increased risk for RSV bronchiolitis and incomplete protection from passive RSV immunotherapy (Palivizumab).

Genetic Disorders of the Surfactant System

DISEASE PATHOGENESIS/ETIOLOGY: There are currently three genetic disorders of the surfactant system that have been well-described in patients, specifically mutations in SP-B, SP-C, and ABCA3. Also falling into this category are recent descriptions of mutations in TTF1/Nkx2.1 due to the role of this transcription factor in regulating surfactant protein gene expression. Neonatal respiratory distress occurring in term and late preterm infants with no other risk factors for respiratory disease has been described for genetic diseases involving SP-B and ABCA3. (67)(68) Patients with inherited deficiency of SP-B exhibit combined deficiency of both SP-B and SP-C due to aberrant post-translational processing of the SP-C proprotein, which seriously impairs the bioactivity of the alveolar surfactant. (69) ABCA3 (an ATP binding cassette protein) is a phospholipid pump that enhances the phospholipid concentration within lamellar bodies. ABCA3 null mutations in mice compromise the function of this pump, reduce the amount of phosphatidylcholine in alveolar surfactant, and compromise the biophysical activity of surfactant. (70)(71)

Other ABCA3 mutations along with familial SP-C mutations are associated with abnormal protein folding, and result in activation of cell stress pathways that contribute to the development of respiratory failure in infancy. (72)(73)(74) Lung disease resulting from these mutations results in alveolar proteinosis and interstitial pneumonitis and is associated with unexplained and progressive oxygen need and tachypnea often in the setting of a normal term delivery and neonatal transition.

CLINICAL TRIALS TO DATE: There have only been anecdotal case reports and small case series describing the use of exogenous surfactant in patients with mutations of SP-B or ABCA3. Although providing short-term improvements in gas exchange, surfactant therapy is not a long-term solution to genetic disorders involving surfactant components. (75)

CONCLUSION: Infants with genetic disorders of the surfactant system are often indistinguishable from late preterm infants with RDS or from term infants with surfactant dysfunction due to neonatal pneumonia. Unless the treating physician is aware of a prenatal diagnosis or family history of one of these genetic disorders, it is understandable that these infants will initially be treated with surfactant due to their clinical presentation. However, there is no evidence base supporting the continued use of surfactant in these patients.

The Future of Surfactant Therapy

At present, RDS is the *only* FDA-approved indication for the use of exogenous surfactant. Any other potential uses (as described above) are considered off-label, and if undertaken should include full disclosure of the perceived risks and unclear benefits. The evidence for surfactant

therapy in the treatment of RDS is strong, and yet many infants with a diagnosis of RDS do not receive surfactant therapy. A recent study utilizing the Pediatric Health Information Systems database demonstrated that only 46% of infants born at 30 to 34 weeks gestational age and given a diagnosis of RDS received surfactant therapy. (76) The growing use of noninvasive methods of respiratory support for preterm infants under the best of circumstances could eliminate the need for intubation and mechanical ventilation, making it difficult to also provide exogenous surfactant. Fortunately, there is mounting evidence that as long as the preterm lung is adequately recruited, delayed surfactant administration for those infants failing CPAP does not result in increased rates of BPD. (77)(78) Additionally, combination strategies, such as INSURE (intubation-surfactant-extubation) involving brief intubation for the purpose of delivering surfactant before the initiation of CPAP, (79) are gaining popularity.

So where do we go from here? Future developments in surfactant therapy are likely to fall into three categories. *New indications,* as described above, will need to undergo the same rigorous testing as did RDS in multicenter randomized trials before becoming the standard of care. Such studies should be well-grounded in surfactant biochemistry and physiology, and disease pathophysiology, and should heed the important lessons of the past regarding timing of administration to minimize lung injury and dosing intervals. *New delivery methods* are receiving increased attention. Effective nebulization strategies would circumvent the need for intubation, thus bringing surfactant to at-risk patients earlier in their disease process before the onset of extensive lung injury that clearly complicates the effectiveness of surfactant therapy. Finally, *new surfactants* are likely to be developed either with improved efficacy as a surfactant, or with additives designed with specific diseases in mind. Collectins and other proteins of innate immunity may provide passive immunotherapy to preterm infants with reduced SP-A and –D. Incorporation of additives to surfactant would not only expand the indications for surfactant therapy but would provide an effective delivery vehicle for novel therapies (drugs, recombinant proteins, and gene therapy vectors) to the alveolar space.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the effects of surface tension on alveolar and airway stability and lung mechanics (LaPlace law).
- Know the management of RDS, including surfactant replacement.
- Know how to manage meconium aspiration syndrome.

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NeoReviews Quiz

7. The role of pulmonary surfactant deficiency as a cause of respiratory distress syndrome (RDS) in preterm neonates was first reported by Avery and Mead in 1959. Since then, a number of basic and clinical studies have been conducted further delineating surfactant physiology and refining its use in the treatment of RDS. Of the following, the year surfactant was made widely available by the Food and Drug Administration for the treatment of RDS in preterm neonates was:

   A. 1974.
   B. 1979.
   C. 1984.
   D. 1989.
   E. 1994.

8. The first-generation synthetic surfactants contained phospholipid dipalmitoyl phosphotidylcholine, but did not include surfactant proteins SP-B and SP-C. The second-generation animal-derived surfactants contained extracts of minced bovine or porcine lung, or from lung lavage. The third-generation newer surfactants contain engineered protein components that mimic the structure and function of SP-B and SP-C. Of the following, the newest surfactant that contains a synthetic amino acid peptide consisting of successive repeats of one leucine and four lysines designed to mimic the properties of SP-B is:

   A. Curosurf.
   B. Exosurf.
   C. Infasurf.
   D. Surfaxin.
   E. Survanta.

9. Surfactant is most effective when delivered before the onset of lung injury. Direct effects of lung injury on alveolar surfactant include inactivation, degradation, conversion to other structural forms, and inhibition of function. Indirect effects of lung injury include suppression of synthesis of surfactant constituents by alveolar type 2 epithelial cell. Of the following, the surfactant degradation is *most* likely caused by:

   A. Inflammatory cytokines.
   B. Lipases.
   C. Oxidants.
   D. Plasma lipids.
   E. Plasma proteins.

10. Homogeneous distribution of surfactant over a large surface area of the lung is critical to the success of treatment. Of the following, the optimal distribution of surfactant is *most* likely using:

    A. Assisted ventilation to optimize airway and alveolar patency.
    B. Diuretic treatment for lung liquid clearance.
    C. Gravity-assisted maneuvers.
    D. Slower rate of administration.
    E. Smaller volume of dose.

11. The use of surfactant in the treatment of neonatal lung diseases other than respiratory distress syndrome may be warranted based on the surfactant pathophysiology of these diseases. Of the following, the function of hydrophilic surfactant proteins SP-A and SP-D provides the best rationale for surfactant treatment in:

    A. Bronchopulmonary dysplasia.
    B. Congenital diaphragmatic hernia.
    C. Genetic surfactant disorders.
    D. Infectious bronchiolitis.
    E. Meconium aspiration.

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