Published in final edited form as:
Ther Deliv. 2013 August ; 4(8): . doi:10.4155/tde.13.72.

Delivery and performance of surfactant replacement therapies to treat pulmonary disorders

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Abstract

Lung surfactant is crucial for optimal pulmonary function throughout life. An absence or deficiency of surfactant can affect the surfactant pool leading to respiratory distress. Even if the coupling between surfactant dysfunction and the underlying disease is not always well understood, using exogenous surfactants as replacement is usually a standard therapeutic option in respiratory distress. Exogenous surfactants have been extensively studied in animal models and clinical trials. The present article provides an update on the evolution of surfactant therapy, types of surfactant treatment, and development of newer-generation surfactants. The differences in the performance between various surfactants are highlighted and advanced research that has been conducted so far in developing the optimal delivery of surfactant is discussed.

Mammalian lung bifurcates into many bronchi and bronchioles ending with alveoli, where gas exchange occurs. The numerous alveoli in the lung provide an extensive surface area (~75 m^2 for an adult lung), mediating efficient gas exchange between epithelial cells and the capillaries in the alveolus [1,2]. The alveolus represents a dynamic physical structure characterized by a high surface tension created by a thin layer of water in the alveolus. The work done to expand and contract the lung against this high surface tension would contribute to a significant drain on the metabolic energy. Fortunately, the alveoli are coated with a thin film of pulmonary surfactant (surface active agents) that regulates the interfacial tension in the lung, minimizing the work of breathing as well as insuring uniform lung inflation [3].

Basic properties & composition of pulmonary surfactants

In order to maintain the integrity of the alveolus during exhalation, the surface tension in the lung should reduce to nearly zero such that a positive pressure difference is maintained between the alveolus and the outside. Additionally, a healthy lung surfactant must allow rapid adsorption and spreading at the air–water interface in the lung, during the inhalation

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Financial & competing interests disclosure
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

process. In simpler terms, an efficient lung surfactant must be able to be rigid enough to resist collapse at exhalation, and also be fluid enough to spread and cover the alveolar surface at inhalation. No one biological component is able to perform both these functions, which explains the presence of saturated and unsaturated lipids and proteins in **pulmonary surfactants**. Synthesized and recycled by alveolar epithelial type II cells (also known as type II pneumocytes), pulmonary surfactant is stored in lamellar bodies, and secreted into the airspace as tubular myelin, from which it is then adsorbed into the air–water interface to form a surfactant monolayer. Surfactant components are recycled via receptor-mediated endocytosis, reincorporated in lamellar bodies and then re-secreted. The membrane receptor, A3, belonging to the ABCA3 family, plays a significant role in this cycle [4]. During these different stages of the surfactant life cycle, the surfactant components exist in several different stages: lamellar bodies (size: 500 nm–1–2 μm), nanotubes (height: 2–5 nm), monolayer films (height: 0.8–5 nm) and multilayered reservoir phases [5]. Approximately 90% of surfactant is conserved during this cycle and the entire circulating surfactant pool is replenished every 9–10 days.

Pulmonary surfactant is composed of approximately 90% lipids, and 10% proteins. The dominant phospholipid is disaturated dipalmitoylphosphatidylcholine (DPPC, 30–70%) with smaller fractions of unsaturated phosphatidylcholine (PC, 25–35%), anionic phosphatidylglycerol (PG), and minor fractions of phosphatidylethanolamine and sphingomyelin. Native lung surfactant also has four surfactant proteins, SP-A, SP-B, SP-C and SP-D. Surfactant proteins SP-B and SP-C are critically important hydrophobic proteins responsible for surfactant adsorption and helping to attain low surface tension [6]. SP-B and SP-C are encoded on human chromosomes 2 and 8, respectively, and are initially synthesized as large precursor proteins, proSP-B and proSP-C, respectively. They are further processed proteolytically in the airspaces to mature forms of SP-B and SP-C. SP-A and SP-D are hydrophilic glycoproteins that are members of the calcium-dependent carbohydrate-binding collectin family of host defense proteins. They are encoded on human chromosome 10. There are two genes for SP-A (*SFTPA1* and *SFTPA2*) and one for SP-D (*SFTPD*) [4].

Overview of the molecular mechanism of surfactant function

While DPPC lowers the surface tension to near zero when fully compressed, it fails to adsorb from solution and re-spread at the necessary rate when the compression is relieved. This explains the presence of unsaturated lipids such as PG and PC, which fluidize the monolayer, as well as the amphiphilic proteins SP-B and SP-C that work together to promote adsorption and spreading during dynamic compression-expansion cycling [7]. The more fluid monolayers cannot achieve the low surface tensions necessary for lung function. It is therefore thought that the unsaturated lipids and proteins are ‘squeezed-out’ of the monolayer to the sub-phase during expiration, such that they remain near the interface in a ‘surface associated reservoir’, and can efficiently re-adsorb during inspiration. This ‘surface associated reservoir’ is possibly linked to the monolayer by proteins SP-B and SP-C [8]. While both SP-B and SP-C appear to be critical, congenital SP-B deficiency is lethal, while congenital SP-C deficiency is associated with chronic interstitial lung disease. Hydrophilic surfactant proteins SP-A and SP-D are significantly involved in pulmonary host defense and the control of lung inflammation. They can bind microorganisms and modulate 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, thus regulating surfactant recycling and secretion [9]. SP-D plays an intrinsic role in surfactant reuptake and recycling and has potent protective properties as an antioxidant. Lack of SP-A increases the susceptibility to pulmonary infections by bacteria and viruses. However, SP-D deficiency can result in spontaneous emphysematous change

and the development of pulmonary fibrosis, revealing a critically important role for SP-D, in particular, in the control of lung inflammation [10].

In summary, the complex mixture of lipids and proteins that make up the pulmonary surfactant work together to minimize the work of breathing as well as insuring uniform lung inflation. The surfactants are capable of efficiently lowering the surface tension at end expiration and maintaining a fluid film capable of adsorption and spreading during the inhalation process. It is therefore not surprising that a deficiency or dysfunction of lung surfactants leads to several different respiratory diseases.

Mechanisms of surfactant deficiency or dysfunction

Lungs are one of the last organs to develop and mature during the gestation period. Therefore, the primary cause of respiratory distress syndrome (RDS; <28 weeks in humans) in very preterm infants is due to a deficiency of the surfactant pool. On the other hand, surfactant deficiency or dysfunction can be a result of mutations in the gene associated with surfactant synthesis or due to non-genetic factors affecting the surfactant pool. For example, **surfactant dysfunction** as a result of deficiency of protein SP-B results in respiratory failure generally within 3 months of birth. Neonatal lung disease could also occur as a result of mutations in genes encoding ABCA3, thereby affecting the transport of surfactant lipids into the lamellar body [4,11–13]. Lung disease associated with SP-C gene (*SFTPC*) mutations is inherited in an autosomal dominant fashion such that one allele is sufficient to cause disease. However, the age of onset and severity of disease can vary. The effect of SP-C deficiency on the lung disease may be less compared with the effect induced by the production of mutant protein which can be toxic [4,14].

Direct and indirect lung injury can result in the dysfunction of lung surfactant [2]. The most common mechanisms of surfactant dysfunction are alterations in the surfactant structure (change in the ratio of small and large surfactant aggregates), chemical alteration of the surfactant constituents and changes in the alveolar type II pneumocytes (cells associated with lung surfactant metabolism), thereby affecting the synthesis or secretion of the surfactant or loss of biophysical activity of the surfactant constituents due to inhibition by other biomolecules [15]. Most common surfactant inhibitors are plasma proteins, lysophospholipids, free fatty acids, high levels of cholesterol, reactive oxygen species (free radicals), pollutants (acid, chemical fumes) and enzymes (proteases and phospholipases) [16].

The two primary mechanisms of surfactant inhibition by surfactant inhibitors are the competition between different molecular species for the air–liquid interface and alteration of the surfactant film. Common conditions include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), meconium aspiration syndrome (MAS) and pulmonary edema. Permeability of the alveolar capillary membrane increases in pulmonary hemorrhage (PH) or hemorrhagic pulmonary edema resulting in the leakage of plasma proteins (albumin, fibrinogen and hemoglobin) into the alveolar space thereby causing surfactant dysfunction. These water soluble plasma proteins are also capable of spontaneously adsorbing to the air–water interface by molecular diffusion. Owing to their smaller sizes they can compete with the surfactant aggregates for the air–water interface. Once at the interface, these proteins form a thin film that acts as a steric and/or an electrostatic energy barrier preventing the adsorption of the surfactant constituents. Since plasma proteins cannot lower the surface tension as efficiently as pulmonary surfactant, inhibition of the pulmonary surfactant by plasma proteins affect the surfactant function. Gunasekara *et al.* reported that the inhibition of lung surfactant by serum proteins is not due to competitive adsorption alone but can also be due to alterations in the surfactant itself [17].

Unsaturated membrane phospholipids (PLs; lysolipids), free unsaturated fatty acids, bile acids and cholesterol (meconium), are capable of mixing with the pulmonary surfactant and altering the structure of the monolayer film at the air–water interface. The altered composition and packing causes the pulmonary surfactant to lose its ability to maintain a condensed structure at end expiration. Biophysically, this inability corresponds to a failure to reach ultra low surface tensions required at end expiration. For example, it has also been reported that DPPC was inactivated at pH ranging from 2.6 to 0.4, thereby affecting surfactant adsorption [18]. This type of inhibition can sometimes be overcome by increasing the surfactant concentration [16].

Cholesterol is a particularly interesting neutral lipid component of the lung surfactant. While it has been a part of the natural surfactant in small amounts and does not seem to alter the biophysical activity (<5 wt%), the surfactant function is altered at higher physiological levels (>10 wt%). For instance, there have been reports of its increased levels in acid lung injury, ventilation and oxidant induced ARDS. However, the mechanism of cholesterol induced inhibition is still not clearly understood [16]. At levels above 10%, cholesterol affects the crystalline packing of DPPC domains such that it gets intercalated in between the aligned, saturated aliphatic tails of DPPC affecting the ability of the interfacial surfactant film to reach near zero surface tension upon maximum compression [19–21].

Enzyme-induced hydrolysis of surfactant constituents can also cause loss of biophysical activity of surfactant. Enzymes like phospholipase or protease can act as potent surfactant inhibitors. Peroxidation of surfactant lipids by reactive oxygen species may affect the surfactant function as well [15].

Overview of exogenous surfactant replacements for pulmonary diseases

Surfactant replacement therapy has emerged as an effective and safe therapy for immaturity-related surfactant deficiency since its introduction in the late 1980s. Randomized, controlled trials have confirmed that surfactant replacement reduces initial inspired oxygen and ventilation requirements as well as the incidence of RDS, death, pneumothorax, and pulmonary interstitial emphysema. This therapy may also be effective in other lung diseases such as MAS, neonatal pneumonia, ARDS and ALI [22,23]. The success of this therapy mainly depends on surfactant composition, formulation process, and efficient delivery to targeted regions of the lung with uniform distribution.

The delivery of exogenous surfactant in infants could be prophylactic or rescue. The prophylactic surfactant approach includes surfactant delivery before the onset of respiratory symptoms. This approach offers the theoretical advantage of a more homogeneous surfactant distribution, a decrease in need for mechanical ventilatory support thus minimizing barotrauma and lung injury. It has mainly been used in clinical studies as surfactant delivery within a time frame of up to 30 min after birth. Conversely, the rescue surfactant approach reserves surfactant for neonates with established RDS, most commonly within the first 12 h after birth when prespecified threshold criteria for RDS are met. This technique offers the theoretical advantage of only treating infants with clinical disease thus avoiding the possible risks and costs of treating infants that would not need to be treated [24,25].

Exogenous surfactants have undergone extensive testing in a huge number of well-designed, carefully controlled, and properly randomized clinical experiments before US FDA approval for human use [26]. There are several kinds of exogenous surfactants and the selection of surfactant type is still not completely resolved **(Table 1)**. Almost all of the currently used exogenous surfactants have a high efficacy in treating neonatal respiratory distress syndrome

(NRDS), yet almost none of them are as successful in treating surfactant dysfunction, particularly in adults. **Tables 2–6** demonstrate the effect of exogenous surfactants on most common neonatal pulmonary disorders, such as NRDS, MAS, congenital diaphragmatic hernia and PH. Additionally, **Table 7** covers the less common disorders including ALI, ARDS, acute hypoxemic respiratory failure, chronic lung disease (CLD), bronchopulmonary dysplasia (BPD), severe bronchiolitis and pneumonia and pulmonary alveolar proteinosis. The current status of surfactant therapy indicates that more research is required towards attaining a better understanding surfactant dysfunction mechanisms, biophysical functions or surfactant delivery techniques. In the rest of this section, the authors focus on the composition of the different classes of exogenous surfactants currently used in therapy.

Human surfactant

Human amniotic fluid is the protective liquid contained in the amniotic sac of a pregnant female. It contains all surfactant constituents and is highly resistant to inactivation but it is not readily available [27]. King and co-workers reported the presence of SP-A in pulmonary surfactant isolated from human amniotic fluid that was obtained at term cesarean sections [28]. Hallman *et al.* studied the effect of a sterile, human surfactant complex derived from amniotic fluid on respiratory failure of very low-birth-weight infants with severe RDS. They investigated an immediate improvement when human surfactant was delivered intratracheally to the airways of infants but the duration and magnitude of the effect was variable. This study suggested that this type of surfactant could modify favorably the severity of RDS in some infants when administrated within 6 h of birth [29].

In 1985, the same scientists tested the efficiency of human surfactant treatment in a randomized prospective clinical trial. Their observations demonstrated that surfactant treatment at, or soon after, birth might distribute the instilled surfactant more evenly, by improving its clinical efficacy, and might decrease lung injury and the occurrence of BPD [30]. These results were confirmed by other studies that concluded a promising effect of human surfactant on survival of very premature infants suffering from surfactant deficiency as well as the reduction of pulmonary sequel of RDS [31–34]. Human surfactant may also reduce ventilator requirements and the incidence of pulmonary air leaks.

Animal derived surfactants

These surfactants consist of lipid extract preparations obtained from either bovine or porcine sources **(Table 1)**. Common components are saturated and unsaturated PLs, mainly consisting of PC and PG head groups, and the hydrophobic surfactant apoproteins, SP-B and SP-C. These surfactants have been carefully evaluated in numerous clinical trials for the treatment of NRDS **(Table 2)**. They have also been used in experimental models and clinical trials for the treatment of other diseases, such as ARDS, MAS and bronchiolitis, with encouraging results in some cases **(Tables 4–7)**.

Due to the biochemical and functional differences between animal-derived surfactant preparations, several studies have been conducted to compare their safety and efficacy **(Table 3)**. Some researchers designed pilot trials to compare treatment regimens of the bovine preparation; Survanta® and Alveofact®, and the porcine surfactants; Curosurf®, in NRDS. Alveofact, and Curosurf treatment regimens resulted in a more rapid improvement in oxygenation than Survanta and reduced ventilatory requirements up to 24 h after starting treatment. This was also a trend towards reducing the incidence of air leaks and severe intracranial hemorrhage in babies who were receiving porcine surfactants [35]. However, no differences in mortality and morbidity were observed among the three groups. These findings were confirmed in larger randomized, controlled trials [36]. The lung pharmacokinetics of two bovine surfactants of different composition (Survanta and

Alveofact) were also studied in airway specimens from small preterm neonates who were mechanically ventilated for 5–7 days. The data demonstrated that surfactant clearance and metabolism depended on the type of bovine surfactant preparation delivered [37].

Biophysical and animal testing demonstrated that Infasurf® developed lower surface tension and reinstated total surfactant activity better than Survanta. The major compositional differences between the two surfactants are: Survanta has relatively higher levels of non-PC PLs (sphingomyelins and phosphatidyl-ethanolamines) as well as additives such as palmatic acid with negligible amounts of SP-B. Infasurf, on the other hand, contains large amounts of SP-B and SP-C, as well as up to approximately 5 wt% cholesterol. Treatment with Infasurf was more beneficial and exhibited a longer effect than Survanta in ARDS; however, no difference in mortality between infant groups was noted [38].

The PC molecular compositions obtained in porcine surfactant are closer to those in human surfactant suggesting that porcine lungs would be more suitable for development of exogenous surfactants [8]. Exogenous surfactants made by using bronchoalveolar lavage were found to be more resistant to inhibition induced by serum proteins as compared with those made using minced lungs. Recent results from our group also demonstrate that surfactant protein SP-B interacts primarily with the negatively charged PG lipids, which may explain the benefit of using increased concentrations of PG in replacement surfactants [39].

Synthetic surfactants

Protein free synthetic surfactant (lipid-based)—DPPC, the main component of pulmonary surfactant, can efficiently lower the surface tension to near zero. Its effective surface-active properties and its lack of interference with the normal formation of the pulmonary surfactant were actually the main reasons for its tentative use as surfactant replacement therapy. Scientists delivered synthetic β-γ dipalmotyl-L-α-lecithin as microparticulate aerosols to rats and observed a decrease in alveolar surface tension [40]. In another study, it was administered by microaerosolization to 11 infants suffering from RDS. In eight of the treated infants who survived, RDS was alleviated; however, the results were inconclusive and needed further investigation [41]. In a pilot study, a sonicated mixture of DPPC/dipalmitoyl PG (9:l) vesicles was nebulized and administered to 13 infants with RDS. Preliminary results of the controlled study suggested an improvement in the level of PL but not an accidental improvement in the disease [42]. Fujiwara *et al.* developed artificial surfactant with the same properties as native pulmonary surfactant. It consisted of a mixture of naturally occurring surfactant lipids and synthetic lipids containing DPPC and PG in the molar ratios of 1:0.65:0.12. This surfactant improved pulmonary mechanics in premature rabbits and protected their immature lung due to intermittent positive-pressure. When delivered endotracheally to infants with RDS, this surfactant prevented progressive lung disease [43]. Artificial lung surfactant (ALEC®) containing pure DPPC and PG in a ratio of 7:3 was also prepared as dry powder and blown down an endotracheal tube (ETT) into the lungs of very premature babies at birth. The results suggested that this surfactant in a dry form may turn out to be effective substitute surfactant in premature babies [44].

Although many experiments and clinical trials have been performed, DPPC and PG have proved uniformly ineffective in treating NRDS because these lipids alone may adsorb slowly. Subsequently, several investigators have used Exosurf® as a surfactant replacement therapy. It is an FDA-approved protein-free synthetic surfactant that is composed of DPPC, to lower surface tension, hexadecanol to accelerate adsorption, and tyloxapol to facilitate dispersion. This surfactant is able to decrease the severity of NRDS. Rescue use of Exosurf can also improve the morbidity and mortality rates for premature infants with RDS. In

addition, cases of PH diagnosed at autopsy were found to occur less frequently in infants treated with Exosurf [45]. Unfortunately, Exosurf is currently not being produced.

Synthetic surfactants including lipids & surfactant proteins—Advances in surfactant therapy research have led to the development of more advanced synthetic surfactants, merging synthetic lipids with synthetic protein analogs based on human-surfactant protein sequences. These surfactants demonstrated promising results in animal and human trials. For example, it is well-known that SP-B (79 amino acids) belongs to the saposin protein superfamily, and plays functional roles in lung surfactant. The disulfide cross-linked, N- and C-terminal domains of SP-B have been theoretically expected to fold as charged, amphipathic helices, indicating a potential role in surfactant activity. Surfaxin®, an engineered synthetic surfactant, contains sinapultide (KL_4), a human peptide analog of human SP-B, based on the amphiphilic C-terminal region, that was recently approved by the FDA (March 2012). KL_4 appears to be more resistant to protein inhibition and oxidative stresses compared with human SP-B. When formulated in an aqueous dispersion with DPPC and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol, KL_4 creates a strong and durable surfactant activity as confirmed by expansion of pulmonary alveoli and improvement of gas exchange in NRDS [46]. Surfaxin is intended for use in diseases characterized by absent, diminished or inactivated surfactant such as NRDS, ARDS, MAS, BPD, asthma and pneumonia. Successful trials indicated that bronchoscopic ‘cleansing’ of the lungs with dilute Surfaxin may offer a safe and feasible approach to improving outcomes in patients with ARDS [47]. Recently, Sáenz *et al.* investigated the vital protective role of intratracheal delivery of KL_4 surfactant in reducing ischemia-reperfusion injury after lung transplantation [46].

Structural studies with Mini-B, another peptide analog of SP-B containing a disulfide-linked construct based on both the N- and C-terminal regions of SP-B, indicated that these neighboring domains are helical and Mini-B retains critical *in vitro* and *in vivo* surfactant functions of the native protein [48,49]. Parallel analyzes were performed on Super Mini-B, having native SP-B residues attached to the N-terminus of Mini-B, to test whether the N-terminal sequence was also involved in surfactant activity. The results demonstrated that Super Mini-B displayed an improved surfactant activity, owing to the self-assembly of monomer peptide into dimer Super Mini-B that mimics the functions and putative structure of native SP-B [50].

Synthetic SP-C analogs were also found to be capable of forming effective surfactants. Venticute® is a synthetic surfactant containing 2% modified human rSP-C (with native poly-Val sequence), DPPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol and palmitic acid. In patients with ARDS, treatment with rSP-C surfactant resulted in improved blood oxygenation after up to four ETT instillations of the surfactant [51]. It can improve lung function in premature newborn rabbits and lambs as well as in animal models of ALI. There is evidence that Venticute may be safely administered to patients with ALI [52]. The activity of synthetic surfactants containing a poly-Leu SP-C analog (SPC33) was also evaluated in ventilated premature newborn rabbits and demonstrated similar improvement in lung function to Venticute [53].

SP-A and -D have multiple functions in immune defense and regulation in the lung. Walther *et al.* used the hydrophobic moment algorithm to identify amphipathic segments of human SP-A, which could play functional roles in lung surfactant. From this ana lysis, they synthesized a 31-residue synthetic peptide with an amino acid sequence based on residues 114–144 of native SP-A ($A^{114–144}$), and confirmed *in vitro* surface activity and *in vivo* efficacy when included in lung surfactant dispersions [54]. It has also recently become possible to generate recombinant forms of SP-D in large amounts that could be useful

therapeutically in attenuating inflammatory processes in neonatal CLD, cystic fibrosis and emphysema. There is a need for further investigation to assess the potential benefits of this surfactant in a clinical setting [55].

Some researchers have also established the addition of polymer and polyelectrolytes such as hyaluronan, PEG or chitosan to substantially improve the surface activity of surfactants, particularly when used to treat ARDS. For example, hyaluronan, dextran and PEG have been added to KL_4 surfactant [21,56]. These results proposed that future *in vivo* studies are reasonable and may allow the engineering of new surfactant formulations that may be effective in diseases with significant protein leak into alveolar spaces. The new synthetic peptide–polymer surfactants would have the benefits of increased reproducibility, improved safety, and probably reduced cost [57].

Differences in molecular properties & performance of pharmaceutical surfactant systems

In general, surfactants with hydrophobic proteins produce more rapid improvement in NRDS, and are less sensitive to inhibition by serum proteins and other substances that accumulate in injured lungs compared with lipid-based synthetic surfactants. Synthetic surfactants are encouraged as being more uniform in composition, less expensive and safer than natural surfactant. Even though animal-derived surfactants have better biophysical properties than lipid-based synthetic surfactants, they demonstrate a possibility of immunological consequences to foreign proteins and some theoretical risks of disease transmission such as bovine spongiform encephalopathy. In addition, manufacturing inconsistencies based on the variability of their sources have also been described [10]. When numerous comparison trials were assessed by meta-analysis, animal-derived surfactants were demonstrated to be more effective, accompanied with a large decrease in occurrence of pneumothoraxes and a possible decrease in neonatal mortality compared with lipid-based synthetic surfactants [58,59].

Bernhard *et al.* implemented a comparative study on the functional, biochemical and morphologic variances of several commercial surfactants in relation to native bovine and porcine surfactants [60]. It was obvious that increasing calcium content of the aqueous mixture to nonphysiological concentrations artificially improved the activity of Alveofact and Curosurf, but had minor effect on Exosurf and Survanta. The surface activity of commercial surfactants was impaired compared with native surfactants due to the lack of surfactant protein SP-A and reduced amounts of SP-B/C. The higher surface activity of Curosurf compared with Alveofact was probably due to its higher DPPC concentration. In spite of the large DPPC content of Survanta and Exosurf, they exhibited poor surface activity possibly due to low or negligible amounts of SP-B/C. Structurally, Curosurf and Alveofact consisted mainly of lamellar and vesicular structures, which were also found in native bovine and porcine surfactants. Exosurf had crystalline structures only, whereas the DPPC-enriched Survanta contained separate lamellar/vesicular and crystalline structures. This study confirmed that *in vitro* surface activity of commercial surfactants was decreased compared with native surfactants at physiological calcium concentrations and, in the presence of SP-B/C, the surface activity is dependent on the DPPC concentration.

Most exogenous surfactants have at least one of the hydrophobic surfactant proteins (SP-B and SP-C) [15]. Exogenous surfactants with higher concentrations of SP-B and SP-C demonstrated better biophysical properties. Higher concentration of SP-B in the exogenous surfactant was also found to be responsible for imparting antibacterial properties against *Escherichia coli* and Group B *Streptococcus* [8]. The resistance to inhibition of the exogenous surfactants could also depend on the amounts of SP-B and SP-C. Compared with the endogenous bovine surfactant, Survanta contains approximately 1/8 SP-B and 1/2 SP-C. Curosurf contains approximately 1/3 SP-B and 1/2 SP-C (compared with the endogenous

porcine surfactant) [16]. Many trials have also been investigated to identify analogs of the two hydrophobic pulmonary surfactant proteins SP-B and SP-C to formulate a synthetic surfactant preparation for the treatment of different pulmonary disorders. A new synthetic surfactant containing both SP-B and SP-C (CHF 5633) analogs demonstrated significant benefit over animal derived surfactant in an *in vivo* model of surfactant inactivation in premature lambs [61,62].

In 2001, an *in vitro* study was conducted to compare the inhibitory effects of human meconium on different surfactant preparations: namely, Curosurf, Alveofact, Survanta, Exosurf, ALEC, rabbit natural surfactant from bronchoalveolar lavage and SP-C surfactants, including Venticute or a leucine/lysine polypeptide. The results revealed that SP-C surfactant was more resistant to inhibition than the modified natural surfactants but less resistant than natural lavage surfactant containing SP-A. This may indicate that recombinant hydrophobic surfactant proteins or synthetic analogs of these proteins can be used for the design of new surfactant formulations that are comparatively resistant to inactivation and therefore suitable for ARDS treatment [63]. Subsequently, findings from a 1-year follow-up study, as well as data from several original reports of Surfaxin trials, have strongly suggested that Surfaxin delivery to infants at risk of RDS resulted in neonatal survival that was at least comparable, if not superior, to that of infants administered Survanta and Curosurf. Moreover, there was no difference in morbidity through 1 year corrected age in infants given Surfaxin versus other natural surfactants in spite of the comparably higher number of survivors [64].

Pulmonary surfactant is heterogeneous and can be divided into different subtypes on the basis of its ultrastructure, biophysical behavior, and composition [65]. Larger or heavy surfactant subtypes have tubular myelin, lamellar bodies, and large vesicles, while the smaller or light subtypes contain primarily small vesicles. Large surfactant aggregates have a greater ability to lower surface tension compared with small aggregates. Recent results indicate that modification in the quantity and surface activity of the surfactant subtypes in the lung can be another mechanism of surfactant inhibition. Surfactant conversion into subtypes is clinically important as this process is expected to occur naturally and surface activity varies depending on the subtype [66,67]. *In vitro* studies have demonstrated that conversion rates of heavy to light subtypes increase with the addition of serum. In light of this, serum is expected to negatively affect surfactant activity [67]. Manalo *et al.* studied the differences in subtype conversion of Survanta and KL_4 surfactant. The effect of fibrinogen on subtype conversion, and the subsequent change in activity, was also explained. The results revealed that these surfactant formulations have various subtype conversions when exposed to surface area cycling and in the presence of fibrinogen. These conversions led to different activities toward lowering surface tension. Manola and co-workers speculated that endogenous fibrinogen will also affect these two surfactants differently *in vivo* and thus influence their clinical effectiveness [68].

Delivery methods of pulmonary surfactant therapy

Currently, research efforts are directed to the fine-tuning of surfactant therapy. Successful delivery of pharmaceutical surfactant therapy to the lung still presents a significant challenge. Many diverse technologies have been used to deliver the exogenous surfactants to the lungs. These technologies range from traditional techniques such as endotracheal instillation, to more recent technologies like inhalation.

Intratracheal instillation

The most common method of delivery is the direct instillation of surfactant suspension into the patient's lung through a side port adapter attached to ETT. Endotracheal intubation is the

only established means of sufficiently delivering surfactant to the lungs of infants, children, or adults with respiratory failure [69]. The targeting of the surfactant liquid can be affected by several factors such as the physical properties of the liquid, the interfacial activity, the gravitational orientation, instillation method, and spread rapidity. Surfactant can be delivered by rapid instillation or slow instillation [45,70]. Rapid instillation was demonstrated to be more efficient in several clinical experiments. Instillation of surfactant delivery at a slow rate of ventilation could result in a non-homogeneous surfactant distribution. This could lead to over-inflation of only parts of the lung receiving the surfactant while other alveoli remain collapsed. Over-inflation of the alveoli can cause injury resulting in BPD. Conversely, a more uniform vertical distribution of surfactant liquid throughout the lung was obtained with the higher ventilation rate [71].

Two delivery methods to instill surfactant liquid in a rat lung model have been reconnoitered by Cassidy *et al.* [72]. In the first method, the instilled liquid is primarily driven by gravitational drainage, followed by inspiration, while in the second method; a liquid plug is permitted to form in the trachea, which is then driven to the distal parts of the lung by ventilation. It was concluded that the instilled liquid, in the second method, reached the distal regions of the lung very quickly (in a few breaths), leading to a more uniform liquid distribution throughout the lung. However, in the first method, the liquid drainage at a bifurcation is reliant on the alignment of the airways with respect to gravity, the branch angle and the relative size of parent to daughter tubes [72]. It was discovered that a 1 min dosing procedure of Curosurf by a dual-lumen tracheal tube without ventilator disconnection could reduce dose problems [73].

There are some concerns about the safety and efficacy of this delivery method. The procedure is associated with non-uniform distribution of the surfactant, and a high dosage regimen is required, which surpasses the amount of the endogenous surfactant pool. Rapid fluctuations in hemodynamics and cerebral perfusion following surfactant instillation have also been described [2,74]. Surfactant instillation can be associated with a number of acute side effects such as bradycardia, hypoxia and hypotension [75,76]. For most cases, surfactant is delivered at initiation of, or during mechanical ventilation (MV). MV causes several degrees of ALI, with epithelial disruption followed by fluid leakage and inflammatory response that can inactivate surfactant. Furthermore, surfactant delivery followed by MV may decrease the treatment response with a higher degree of surfactant inactivation compared with surfactant treatment followed by spontaneous breathing. MV has also been considered as the single most significant reason for the late development of BPD [77].

The intubation-surfactant-extubation method

The intubation-surfactant-extubation (INSURE) method, an intubation–surfactant–extubation sequence, is a more recent (late 1990s) effort to reduce the duration of endotracheal intubation. Surfactant delivery by transient intubation with rapid extubation to nasal continuous positive airway pressure (CPAP) offers the benefits of reducing the MV need, the duration of respiratory support, and the necessity for surfactant replacement in preterm infants with RDS. It may be an effective delivery approach to improve regional neonatal intensive care without increasing the need for transportation of moderately preterm infants with RDS [77]. INSURE treatment can also be safely repeated since the respiratory outcome demonstrated no difference between infants treated with single or multiple INSURE processes [78]. Experience, a good CPAP program and ventilator back up are required in the care of these patients. This approach, however, still entails skills for intubation and has the risk of trauma to the glottis and airway during intubation [76].

Emerging advances in delivery

The need to explore novel methods for surfactant delivery methods has emerged as a result of renewed efforts to avoid endotracheal intubation as well as the growing interest in noninvasive ventilation during treatment of respiratory distress. Below, the authors summarize some of the more recent advances in surfactant delivery methods.

Fine nasogastric or catheter tube—This method involves surfactant delivery using a fine gastric tube in spontaneously breathing infants with nasal CPAP. The underlying idea is that inspiring surfactant is more physiologically appropriate than receiving it by positive pressure inflations as with the INSURE procedure. Kribs *et al.* delivered Survanta via an intratracheal catheter to extremely low birth weight infants during spontaneous breathing with nasal CPAP [79]. The catheter was fixed using Magill forceps and was inserted into the trachea using direct laryngoscopy, similar to tracheal intubation. Surfactant was injected over 1–3 min after fixation of the catheter with two fingers and removal of the laryngoscope. After finishing the procedure, the gastric feeding tube was aspirated to avoid the accidental delivery of the surfactant to the stomach [79–82]. In another study, a vascular catheter was inserted through the vocal cords under direct vision without using Magill forceps and surfactant was then instilled, followed by reinstitution of CPAP [83]. The need for laryngoscopy and the use of Magill forceps may limit the use of this approach because of the possibility of injury from both laryngoscope and the catheters. It also potentially needs controlled trials to evaluate its safety and efficacy.

Pharyngeal deposition—Kattwinkel *et al.* have developed an advanced technique of surfactant delivery to preterm infants during birth [84]. The surfactant was injected into the nasopharynx followed by mask- then nasal-CPAP pharyngeal instillation before delivery. The pharyngeal instillation of surfactant before delivery has the potential to replicate the physiologic process. This approach appeared to be safe and simple during vaginal birth. However, the need for a cephalic delivery and a spontaneously breathing infant limit the application of this technique to cesarean section, malpresentation (breech or transverse), or perinatal compromise [76].

Laryngeal mask airway—Since its introduction into clinical practice, the laryngeal mask airway (LMA™) has gained increasing popularity as an innovative method for surfactant delivery. It is a supraglottic device regularly applied to administer positive pressure ventilation in adult, children and neonatal patients. The device consists of a curved plastic tube with an elliptical inflatable mask that is introduced blindly into the posterior pharynx of the baby. The mask may be inflated in the hypopharynx to generate an airtight seal around the upper esophagus. There are different kinds of LMAs (Classic™; ProSeal®; i-Gel™; PAX press™; CobraPLA™) available in the market. Trevisanuto *et al.* instilled Curosurf in aliquots via the LMA followed by brief intermittent positive pressure ventilator after each aliquot [85]. Following surfactant delivery, the LMA was removed and the infant was placed on CPAP for consequent management. The results suggested that the LMA may be used as a conduit to produce a rapid and noninvasive access to the trachea of neonates with RDS to deliver surfactant.

ProSeal LMA has been successfully used by Barbosa *et al.* to deliver surfactant for the treatment of neonates with RDS in Brazil [86]. Some studies indicated similar improvements in oxygenation after surfactant delivery via an LMA compared with an ETT, while device placement required less time and fewer attempts [87,88]. The documented benefits of the LMA involve the ease of positioning, even when performed by relatively inexperienced personnel, and reduced invasiveness when compared with the ETT but controlled clinical trials are needed to confirm its efficacy. There may be a possibility for some adverse effects

including laryngospasm and malposition of LMA. In addition, there is no availability for smaller LMA sizes suitable for extremely premature infants [89].

***In utero* endoscopic delivery—**The feasibility of the endoscopic delivery of surfactant directly to the fetus has been investigated during active preterm labor. A gas-sterilized intraoperative fiberscope was applied through the cervical canal into the amniotic cavity after spontaneous rupture of membranes during preterm labor. Then the surfactant was injected into the mouths of the preterm fetuses through a catheter placed through the biopsy channel of the fiberscope. The worth of intrapartum endoscopy in the prophylactic administration of surfactant directly to the fetus, before the first breath, requires further clinical investigation [90].

Surfactant aerosol delivery

Aerosolized surfactant therapy is a noninvasive technique that is especially appealing to treat the neonatal population. This delivery method has received substantial attention because of its potential superiority over instillation. Aerosols are an attractive approach to deliver drugs for the local treatment of lung diseases as relatively high amounts can be delivered to the site of action, while minimizing exposure to the rest of the body [91]. For example, lower doses of aerosolized surfactant produced effects comparable to higher doses of instilled surfactant, with better distribution of aerosolized surfactant when treating inhomogeneous forms of lung injury [74,92–94]. Some adverse effects on hemodynamics may also be avoided. Additionally, the use of aerosolization procedures allows for full control by the ventilator if desired, which is not available with instillation methods.

Many factors may affect the aerosol delivery of surfactant and the extent of surfactant dispersion after delivery. The design of appropriate devices as well as surfactant preparation for aerosolization to treat intubated and mechanically ventilated infants still offers substantial challenges [91]. Aerodynamic forces are key in distributing aerosol therapeutics within the lungs. The correlation between air flows, aerosol mechanics, and aerosol deposition, which are well characterized in healthy lungs, become more complex in the setting of lung disease [95].

Inhalation of exogenous surfactant in the aerosolized form necessitates four steps to be proficient. First, the surfactant needs to be aerosolized without applying energy that may denature surfactant proteins. Then, the suitable particle or droplet size must be attained so that it is able to penetrate deep into the lung. Third, the particles must be able to re-agglomerate at their site of action and finally, the surfactant has to regain its biological activity upon successful delivery [76].

Several studies have been conducted to address the aspects of safety, efficiency, influence on biophysics, and the composition of surfactant following aerosol delivery. In the past, poor efficiency of aerosol-generating devices in ventilator circuits, insufficient understanding of the factors influencing aerosol delivery during MV, and older models of mechanical ventilators presented major impediments to effective drug delivery. There are also examples suggesting that surfactant delivery by aerosol during spontaneous respiration is less traumatic and prevents the need for intubation with the associated mechanical and infectious threats and pathophysiological effects [92].

The selection of an aerosol delivery device for patients generally depends on many factors including, among others, device/drug availability, clinical setting, patient age and the ability to use the chosen device properly, and drug administration time. In general, the devices used for aerosol generation include nebulizers, pressurized metered-dose inhalers (pMDIs), and dry-powder inhalers (DPIs). Though, metered-dose inhalers and nebulizers are regularly

employed for aerosol delivery to mechanically ventilated patients, exogenous surfactants have also been delivered by nebulizers [96]. **Table 8** compares several trials that have been performed on surfactant as aerosol therapy. As surveyed, the verdict is still out on the efficiency of this technique, but the results indicate that developing more efficient damage resistant surfactant mixtures and delivery techniques may improve the therapeutic potential of this technique.

Nebulizers—Nebulized surfactants have emerged as a therapeutic breakthrough by avoiding the problems of MV; however, only a small amount of nebulized surfactant was anticipated to enter the alveolar space [97]. The recent plan for nebulized surfactant delivery emphasizes the use of an aerosol generator with surfactant delivery by a nasal CPAP system, using either a tight face mask or nasopharyngeal tube [98]. Mass median aerodynamic diameter (MMAD) is a key parameter in determining the delivery of aerosol by inertial, impaction and sedimentary forces. These processes govern movement of aerosols within distinct generations of airway branching and are considered mainly significant for nebulized surfactant delivery [21,75]. It has been reported that the non-sustained effect of surfactant nebulization on oxygenation may be owing to small amounts being deposited and a non-uniform distribution pattern, which may result in non-uniform aeration of the lung [2].

Jet & ultrasonic nebulizers: Both jet and ultrasonic nebulizers have proven successful for aerosol delivery of surfactants during MV. Jet nebulizers normally utilize an electric compressor or a compressed gas source to force air through a nozzle, generating a mist for inhalation. Ultrasonic nebulizers apply a high nebulization rate of a liquid drug formulation, but cannot work efficiently for high viscosity liquids. The effectiveness of aerosol delivery with ultrasonic nebulizers could be reasonably enhanced by using a longer inspiratory time, by reducing the minute ventilation and by employing a lower respiratory rate [21]. Although, ultrasonic and jet nebulizers have been established to be effective and safe in animal models, the therapeutic effects of aerosolized surfactant in human clinical trials have not been significant until now. Most ultrasonic or jet nebulizers require the patient to be on a mechanical ventilator to deliver aerosolized surfactants, however, the inappropriate use of ventilators can cause or enhance lung injury.

Beneficial effects of delivering aerosolized surfactant by CPAP in the treatment of NRDS have been recently reported, in many cases without the need for MV. Jorch *et al.* delivered undiluted natural bovine surfactant by a jet nebulizer via nasopharyngeal tube, which was directly connected via a T-piece to the nebulizer, thus allowing a short distance between nebulizer and the tracheobronchial tree [97]. This CPAP system was only used during nebulization. This pilot study has demonstrated that surfactant delivery to the lung as an aerosol in spontaneously breathing preterm neonates is feasible. Berggren *et al.* also used a jet nebulizer connected directly to the CPAP adaptor in their trial [99]. Research efforts have established that a surfactant aerosol, when delivered as a dried hygroscopic aerosol by ultrasonic nebulizer, can lower the mortality resulted from partial surfactant deficiency in the premature rabbit neonate. This dried aerosol formulation can be delivered by a mask and spontaneously inhaled with sufficient deposition in the suitable regions of the lung to reduce the morbidity associated with RDS. They suggested further trials to find out the most effective means of formulation and drying of the treatment aerosol in addition to studies of its regional deposition [100].

Based on these exciting data, a new noninvasive approach of surfactant-based therapies has been investigated by Sun *et al.* in 2009 [101]. This method depends on inhalation of aerosolized surfactants by spontaneous breathing without intubation or MV, so it may be more efficient in delivering exogenous surfactant into the alveolar space than the other delivery methods.

Vibrating mesh nebulizers: The delivery of aerosolized medications to the lungs via small volume nebulizers has steadily improved through the years. The most recent addition to the small volume nebulizer family is the electronic vibrating mesh (VM) nebulizer. It is exceptional at producing very fine aerosols with higher respirable fractions at slower velocities, all within the shortest delivery times possible. These aerosol delivery devices are able to generate consistently high and effective outcomes due to the way in which the aerosolization occurs. Finer *et al.* tested the feasibility and safety of delivering Surfaxin to newborns with early signs of RDS within 1 h of birth [102]. This study used a clinically approved VM nebulizer, the Aeroneb® Pro (Aerogen, Galway, Ireland), with a specially designed CPAP adaptor that allows for aerosol delivery just below the 'Y' connector. This new nebulizer technology needs only 1 l/min of flow as well as a surfactant formulation that may better survive the exactitudes of nebulization. The process was safe with a low existence of 'peridosing events' but lack of efficiency because of the absence of a control group. Arzhavitina *et al.* compared six different nebulizers in an *in vitro* model [103]. They reported that the VM nebulizer is the superlative device for substances with surface activity, such as surfactants, because the residual volume in the device is negligible and the substance output is maximal.

Comparison studies between instillation & nebulization delivery systems: Nebulized surfactant may avoid or decrease the need for ETT and is well endured, away from transient oxygen desaturation during dosing. There are several trials comparing the effectiveness of nebulized surfactant delivery in animals and the standard instillation approach or other delivery methods **(Table 9)**. The most important observation in studies by Lewis *et al.* was that a relatively small quantity of nebulized surfactant was deposited in severely injured rabbit lung tissues. The amount of nebulized surfactant required for the modest physiological improvements observed were indeed significantly smaller when compared with the quantity required by an instillation technique that was responsible for generating equivalent improvement [92,93,104,105]. Recently, Rey-Santano *et al.* compared the effects of aerosolized surfactant (Curosurf; SF-aero) with those of bolus surfactant (SF-bolus) delivery on gas exchange, lung mechanics, and cardiovascular function in premature lambs with RDS. They demonstrated that SF-aero produced improvements in gas exchange and lung mechanics similar to those produced by bolus administration but with less lung injury and fewer cerebral hemo-dynamic changes [106]. Scientific trials comparing nebulized versus instilled surfactant, in order to inspect both respiratory outcomes and successful treatment of diseases of prematurity, are essential to further assess nebulized efficiency. When the efficacy of nebulization in a neonatal ventilator is improved, then this method of surfactant therapy may be a superior alternative to surfactant instillation.

pMDIs—In mechanically ventilated patients, pMDIs are mainly used to deliver β-adrenergic and anti-cholinergic bronchodilators for treatment of airway obstruction. Because hydrofluoroalkane propellants in pMDIs are incompatible with surfactants, pMDIs are phased out from any trials to deliver exogenous surfactant [107,108].

DPIs—DPIs have gained attention as an attractive alternative to both instillation and nebulization methods in order to achieve consistent and accurate delivery of surfactants to the lungs. These devices have many advantages over nebulizers, such as the capacity to deliver larger doses in much shorter periods of time. DPIs have rarely been used in a ventilator circuit, however, owing to the lack of devices that can work optimally under ventilator conditions. Few trials have been conducted in the past to deliver surfactant as dry-powder formulation. In 1964, synthetic DPPC was delivered by inhalation to rats and a decrease in alveolar surface tension was observed. It was also delivered by microaerosolization to infants with NRDS and the respiratory distress was observed to

improve [41]. Morley *et al.* explored the idea that exogenous surfactant would spread most readily in the airspaces when delivered in dry form [44].

Research scientists have developed a novel dry-powder aerosol of a rSP-C-based surfactant preparation or any other micronized surfactant preparation that meets all requirements for inhalative treatment, in particular for diseases, such as ARDS, in which delivery of a large amount of surfactant is necessary [109]. More recently, Pohlmann *et al.* created a high-concentration continuous powder aerosolization system for inhalable surfactant delivery to preterm neonates. The device is favorable for noninvasive delivery of surfactant aerosol to neonates due to its continuous high-concentration delivery and has the potential for being an adaptable platform, closing the gap between continuously operating nebulizers and discontinuously operating DPI devices [110]. Further investigations are needed to assess the potential of this alternative method for delivery of exogenous surfactant. It is expected that, with additional enhancements to the delivery system, this may make it the technique of choice for pulmonary delivery of surfactants.

Exogenous surfactant as a drug delivery-carrier

Current aerosol medications are mainly dissolved in saline and hence have a high surface tension, which may not allow them to disperse uniformly along the lung airway surface liquid after droplet deposition. In addition, patients with obstructive lung diseases, such as cystic fibrosis, commonly have a greater concentration of delivered medication in the central airway passages than in peripheral regions, based on the unusual aerodynamics associated with partially obstructed flows. Recently, low surface tension carrier fluids have emerged to improve pulmonary drug distribution, provide more reliable peripheral lung dosing, and increase survival in a model of pulmonary infection [103,111]. The success of surfactant replacement therapy has initiated an investigation into using exogenous surfactant to improve the uniformity of aerosolized drug delivery in the lungs. Surfactant-based aerosol carriers can disperse medicines over airway surfaces after deposition through surface tension driven flows, increasing dose uniformity and improving drug distribution into under-ventilated regions [103].

This investigation has been confirmed by Corcoran *et al.,* who exploited a radioscintigraphy technique to track the deposition and redistribution of an inhaled drug analog administered to cystic fibrosis patients in a low-surface tension carrier [95]. Infasurf was employed and paired lung distribution comparisons were made with a size-matched saline aerosol control. Imaging was implemented for 30 min after aerosol delivery. They found that central to peripheral count ratio (c/p) decreased with saline and increased with Infasurf, which may suggest that inhaled Infasurf increased peripheral clearance, due to either surfactant-based dispersion or mucociliary effects [95].

Pulmonary surfactant has also been employed as a vehicle for antibiotic delivery to the alveolar compartment of the lung. Kharasch *et al.* have established that tracheal instillation of ^{99m}technetium sulfur colloid mixed with pentamidine antibiotic in a Survanta vehicle significantly increases airspace deposition of the colloid in healthy hamster lungs, and may improve uniformity of spread [112]. Some scientists discovered increased survival rates of mice with a respiratory *Klebsiella pneumoniae* infection treated intratracheally with tobramycin using a natural exogenous surfactant preparation as the vehicle [113]. It has also been reported that aerosolized Exosurf, alone, potentially increased survival of rats with *Pneumocystis carinii* pneumonia and, when combined with atovaquone, increased plasma and lung concentrations of the drug and eradication of the organism [112]. In this study, the aerosol delivery was done by two aerosol devices; the ‘nose-only exposure system’ and the ‘inhalation exposure chamber’. It was found that the inclusion of surfactant in the

formulation provided almost a twofold increase in the amount of aerosolized atovaquone delivered to the device ports. Finer *et al.* recently stated that highly viscous solutions, such as surfactants, may influence nebulizer output rates, in turn leading to suboptimal emitted dose [102].

Antenatal steroids & surfactant replacements

Glucocorticoids such as dexamethasone and betamethasone are known to be effective in the treatment of ameliorating established CLD. However, their systemic administration to neonates is concomitant with substantial side-effects. Local administration of glucocorticoids by inhalation aerosol and intratracheal instillation represents an alternative route to systemic administration. Because exogenous surfactant is delivered to neonates with RDS, this system is considered as an ideal vehicle for corticosteroid delivery, especially since the addition of corticosteroids does not alter the surface properties of the surfactant [114–116]. Nimmo *et al.* reported that mixing dexamethasone with Survanta did not change the surface characteristics of the surfactant [111]. Moreover, instillation of the dexamethasone/surfactant mixture to rats led to better distribution of the glucocorticoid throughout all four lobes of the lungs, including the peripheral regions.

Preterm delivery has severe morbidity and neonatal mortality including RDS, intraventricular hemorrhage, sepsis and CLD. In 1994, a NIH panel recommended the use of antenatal steroids (AS) in the pregnant women predicted to deliver between 24 and 34 weeks gestation [117]. This treatment was expected to reduce the risk of premature infants developing RDS and intraventricular hemorrhage thereby reducing the mortality by more than 40% and further increasing the efficacy of surfactant therapy. Complete AS course has the maximum beneficial effects if the duration between the initial administration of the therapy and the actual delivery is more than 24 h and less than 7 days. Of course, the efficacy of AS treatment does vary with maternal and the fetal indications before the completion of the treatment. In case of incomplete AS treatment, the infants demonstrated increased incidence of RDS, longer hospital stay and higher rate of intubation in the delivery room compared with the untreated infants.

Future perspective

Exogenous surfactant has been used in the treatment of various pulmonary disorders and is now used as a standard of care in at least some of them. Advances in understanding the mechanisms that impair the lung surfactant system may create innovative rational therapies for pulmonary diseases. The development and evaluation of newer inhibition resistant surfactants, surfactants tailored towards more uniform distribution in the alveolar regions and less invasive delivery techniques, which do not depend on endotracheal intubation, are in progress. Synthetic surfactants based on new protein analogs are a new trend and can be tailored for various clinical situations. There have also been many driving forces over the past few years to develop novel surfactant aerosol therapies and many original devices and delivery techniques have emerged. In addition, the evolution of surfactant therapy has attracted the attention of researchers interested in employing exogenous surfactants to enhance the uniformity of aerosolized drug delivery in the lungs. While much remains to be learned, both clinical and laboratory results continue to generate approaches that might provide novel treatments in the future.

Acknowledgments

A Kaviratna and P Dhar would like to acknowledge support from the Jay Award from the Higuchi Biosciences Center and the NIH (Award number: P20GM103638). N El-Gendy and C Berkland would like to acknowledge support from the Coulter Foundation and the NSF (Award number: CHE 0966614).

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Key Terms

Pulmonary surfactants: Surface-active phospholipoprotein complex formed by type II alveolar cells to increase pulmonary compliance, prevent the lung from collapsing at the end of expiration, keep alveoli dry and regulate its size, and assist in pulmonary host defense.

Surfactant dysfunction: Either a lack of surfactant due to immaturity in premature infants, or due to deficiencies resulting from gene mutations, or due to surfactant inhibition due to injury, inflammation or other non-genetic factors.

Surfactant replacement therapy: Substantially reduces mortality and respiratory morbidity in preterm infants with, or at high risk of, respiratory distress syndrome. It can also be considered for infants and adults with respiratory failure due to surfactant deficiency.

Key Term

Aerosolized surfactant therapy: Noninvasive technique that received substantial attention to treat neonatal pulmonary disorders.

Executive summary

Pulmonary surfactants

- Efficient lung surfactant must be able to be rigid enough to resist collapse at exhalation, and also be fluid enough to spread and cover the alveolar surface at inhalation.
- Surfactant proteins SP-B and SP-C are critically important hydrophobic proteins responsible for surfactant adsorption and to help attain low surface tension.
- Hydrophilic surfactant proteins SP-A and SP-D are significantly involved in pulmonary host defense and the control of lung inflammation.

Surfactant deficiency or dysfunction

- Direct and indirect lung injury can result in the dysfunction of lung surfactant.
- Mutations in gene encoding ABCA3 affect transport of surfactant lipids into the lamellar body.

Exogenous surfactant replacements for pulmonary diseases

- Surfactant replacement therapy has emerged as an effective and safe therapy for immaturity-related surfactant deficiency.
- Successful therapy mainly depends on surfactant composition, formulation process and efficient delivery to targeted regions of the lung with uniform distribution.
- The delivery of the surfactant in infants could be prophylactic or rescue.
- Advanced kinds of surfactants have been developed, merging synthetic lipids with recombinant peptides or proteins based on human surfactant protein sequences.
- The new synthetic peptide–polymer surfactants would have the benefits of increased reproducibility, improved safety and probably reduced cost.

Delivery methods of pulmonary surfactant therapy

- Direct instillation of surfactant suspension into the patient's lung is the most common method of delivery.
- Surfactant instillation is an invasive method combined with a number of acute side effects.
- The intubation-surfactant-extubation method can reduce the duration of endotracheal intubation.
- The pharyngeal instillation of surfactant before delivery can replicate the physiologic process.
- LMA™ can produce a rapid and noninvasive access to the trachea of neonates with respiratory distress syndrome to deliver surfactant.
- Aerosolized surfactant therapy has received substantial attention because of its potential superiority over instillation.
- Jet and ultrasonic nebulizers have proven successful for aerosol delivery of surfactants during mechanical ventilation.
- Dry-powder inhalers can achieve consistent and accurate delivery of surfactants to the lungs.

Exogenous surfactant as a drug delivery-carrier

- The success of surfactant replacement therapy has initiated the exploration of using exogenous surfactant to improve the uniformity of aerosolized drug delivery in the lungs.

Table 1

Classification of exogenous surfactant preparations for pulmonary diseases.

Surfactant source	Material	Proteins	Chemical name	Trade name
Human surfactant				
Human	Amniotic fluid extract	SP-A, SP-B, SP-C		Not readily available
Natural surfactant				
Animal bovine	Modified minced lung extracts[†]	SP-B, SP-C	Surfactant TA Beractant	Surfacten® Survanta®
Animal bovine	Calf lung lavage extracts	SP-B, SP-C	CLSE Calfactant	BLES® Infasurf®
Animal bovine	Cow lung lavage extracts	SP-B, SP-C	Bovactant	Alveofact®
Animal porcine	Minced lung extracts	SP-B, SP-C	Poractant alfa	Curosurf®
Synthetic surfactant (lipid-based)				
N/A	DPPC	None	Nebulized DPPC	N/A
N/A	DPPC-PG[‡]	None	Pumactant	ALEC®[§]
N/A	CPHT	None	Colfosceril	Exosurf®
N/A	DPPC, HDL	None	Turfsurf	N/A
N/A	Apoproteins and synthetic DPPC-DPPG[¶]	None	Aposurf	N/A
Synthetic surfactant (Lipid- and protein-based)				
N/A	N/A	KL_4 (sinapultide)	Lucinactant	Surfaxin®
N/A	N/A	34-residue polypeptide based on SP-B	Mini-B	N/A
N/A	N/A	Dimeric SP-B1-25	Dimeric SP-B polypeptide	N/A
N/A	N/A	rSP-C	Recombinant SP-C (lusulptide)	Venticute®
N/A	N/A	Poly-Leu SP-C analog	SP-C33	N/A
N/A	N/A	N/A	SP-A analogs	N/A
N/A	N/A	N/A	Truncated recombinant fragment of SP-D	N/A

CLSE: Calf lung surfactant extract; CPHT: Colfosceril palmitate (dipalmitoylphosphatidylcholine), hexadecanol (cetyl alcohol) and tyloxapol; DPPC: Dipalmitoylphosphatidylcholine; KL_4: Cationic and hydrophobic 21-residue lysine and leucine peptide; PG: Phosphatidylglcerol.

[†]Minced lungs modified by the addition of phospholipids and fatty acids.

[‡]DPPC-PG at a weight ratio of 7:3.

[§]Artificial lung-expanding compound.

[¶]Reconstituted from isolated low MW (≤15 K) apoproteins and synthetic dipalmitoylphosphatidylcholine and dipalmitoylphosphatidylglycerol.

Table 2

Surfactant therapy for neonates with respiratory distress syndrome.

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
Synthetic DPPC	Inhalation	N/A	Inconclusive results and need further investigation	[41]
DPPC/DPPG (9:l)	Nebulization	No	Failed trial	[42]
A mixture of natural surfactant lipids and synthetic lipids	ETT	Yes	Not randomized	[43]
Artificial lung surfactant contains pure DPPC and PG	ETT (dry powder)	CPAP or IPPV after delivery if needed	Substantially less improvement compared with that achieved with animal surfactant extracts or human surfactant	[44]
Human surfactant	ETT	Yes	Promising treatment for very premature neonates Surfactant treatment at 2 to 4 h after birth is similar to treatment at birth No neurodevelopmental outcomes throughout the first year	[27, 29–32,34]
BLES®	Tracheal	Manual inflations after delivery	Surfactant therapy, before the first breath, is protective against RDS, negative effects of hypoxia and ventilatory support	[118]
BLES	ETT	Yes after delivery	Prevention of RDS in extremely premature infants One dose at birth may not be sufficient Lower incidence of mild CLD with late treatment Significant advantage to the administration of initial dose as prophylaxis rather than as rescue therapy	[119–123]
Exosurf®	ETT	Yes	Rescue use can improve the morbidity and mortality rates Reduced pulmonary vascular resistance, leading to a decrease in pulmonary artery pressure and an increase in ductal flow velocity Beneficial long-term effects. No neurodevelopmental outcome after 1 or 2 year assessment	[45,70, 124–127]
Natural porcine surfactant	Tracheal	N/A	There was immune response after surfactant treatment	[127]
Curosurf®	Boluses into the lower trachea	N/A	No difference between high and low dose surfactant regimens for RDS were noted	[128]
Dexa- or betamethasone + Survanta®	N/A	N/A	Combined use of prenatal corticosteroids and postnatal	[114]

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
			surfactant improved neonatal outcome	
Dexamethasone + human surfactant	Instillation	Manual after dose	Combined use of prenatal dexamethasone with exogenous surfactant improves the outcome	[115]
Curosurf	Intubation	First support by CPAP + manual after each dose	Early treatment of nasal CPAP with single dose of surfactant significantly improves oxygenation and reduces the need for subsequent MV The immediate reinstitution of nasal CPAP after surfactant administration is safe and beneficial	[129–131]
Curosurf	ETT	Yes after delivery	Surfactant is not a vasodilator itself but acts only by improving pulmonary compliance	[132]
Dexamethasone (im.) + Survanta or Exosurf (as prophylactic treatment)	ETT	N/A	Combined use of antenatal dexamethasone and postnatal, surfactant does not decrease the rate or severity of RDS in infants delivered at 24–29 weeks gestation, but may be associated with reduced severity of IVH	[116]
KL_4 surfactant	ETT	Yes	Creates a strong and durable surfactant activity	[133]
Curosurf	Intubation	IPPV	Meta-analysis. Prophylactic treatment has significant advantages over rescue therapy	[134]
Curosurf	1 min dual-lumen ETT	Yes	Curosurf dosing via a dual-lumen tracheal tube without MV disconnection and fractional doses can reduce the number of dosing-related adverse transient episodes of hypoxia	[73]
Curosurf	A modified Aiolos® nebulizer	First supported by nasal CPAP	No beneficial effects contrary to data from animal trials Delivery optimization of aerosolized surfactant is required	[56]
Infasurf®	Nasopharyngeal instillation	Mask then nasal CPAP after delivery	Safe and simple delivery technique, especially for vaginal births	[84]
Survanta	ETT	Yes after delivery	Routine elective intubation for delivery of surfactant to preterm infants having mild to moderate RDS is not recommended	[135]
Curosurf	LMA™	First supported by nasal CPAP	LMA may be a useful and noninvasive conduit for surfactant delivery	[85]

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
			Randomized controlled clinical trial is needed	
Survanta	ETT	Yes after delivery	A prospective observational study of all cases of RDS treated with surfactant during the period from October 2009 to July 2011 The survival of those given surfactant therapy improved with increasing gestational maturity and birth weight Sepsis is an important complication and its presence, along with a high RDS score at intubation are major predictors of mortality	[136]

CLD: Chronic lung disease; CPAP: Continuous positive airway pressure; DPPC: Dipalmitoylphosphatidylcholine; DPPG: Dipalmitoylphosphatidylglycerol; ETT: Endotracheal tube; im.: Intramuscular; IPPV: Intermittent positive pressure ventilator; IVH: Intraventricular hemorrhage; KL_4: Cationic and hydrophobic 21-residue lysine and leucine peptide; LMA™: Laryngeal mask airway; MV: Mechanical ventilation; PG: Phosphatidylglcerol; RDS: Respiratory distress syndrome.

Table 3

Comparison studies of different surfactants for the treatment of neonates with respiratory distress syndrome.

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
Exosurf® versus Survanta®	ETT	Yes for Exosurf Yes after Survanta delivery	A multicenter randomized comparison study No difference in the incidence of death or BPD recorded but a difference in the initial response to treatment was noted	[137]
Curosurf® versus Survanta	Instillation into bronchus	Yes	Curosurf improved oxygenation and reduced ventilatory requirements during the first 24 h compared with Survanta	[35,138]
Survanta versus Alveofact®	ETT	Yes	Pharmacokinetic study Surfactant clearance and metabolism depended on the type of natural surfactant	[37]
Exosurf versus Infasurf®	ETT	Yes	Infasurf provided more effective therapy for RDS Infasurf prophylaxis in the study was associated with a greater risk of total but not severe IVH	[58,139]
Infasurf versus Survanta	ETT	Yes	Infasurf produced longer duration of effect than Survanta The differences in mortality previously reported were not present in a larger, more contemporary data set	[38,140,141]
ALEC® versus Curosurf	ETT	Yes after delivery	Mortality was unexpectedly lower among Curosurf none than among ALEC group	[142]
Alveofact, Curosurf and Survanta	ETT	Yes after delivery	Alveofact and Curosurf were administered by rapid bolus infusion directly into the distal ETT after disconnecting the neonate from MV Survanta was given slowly by pump by a side port adaptor to ETT Alveofact and Curosurf none needed fewer days of oxygenation and on the MV and in hospital than with the Survanta group No differences in mortality and morbidity among the three none	[36]
Surfaxin® versus Curosurf	ETT	Yes	Similar for the prevention and treatment of RDS among preterm infants	[143]
Surfaxin versus Exosurf and Survanta	ETT	Yes	Surfaxin is more effective than Exosurf for the prevention of RDS and reducing the incidence of BPD Surfaxin decreases RDS-related mortality rates, compared with Survanta	[144]
Survanta and Curosurf	ETT	Yes after delivery	Curosurf improved pulmonary outcomes more than Survanta	[145]
Surfaxin versus Exosurf, Curosurf and Survanta	N/A	N/A	The study is 1-year follow-up of very preterm Infants with RDS	[64]

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
			received surfactants demonstrating that Surfaxin is at least as good, if not superior, to animal-derived surfactants for prevention NRDS and may be a viable substitute to animal-derived products	

BPD: Bronchopulmonary dysplasia; ETT: Endotracheal tube; IVH: Intraventricular hemorrhage; MV: Mechanical ventilation; NRDS: Neonates with respiratory distress syndrome; RDS: Respiratory distress syndrome.

Table 4

Surfactant therapy for neonates with meconium aspiration syndrome.

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
BLES®	ETT	Yes	Beneficial in full-term newborns with respiratory failure associated with pneumonia or MAS	[146]
Bovine surfactant extract	ETT	N/A	Effective in full-term infants with respiratory failure due to MAS and RDS A randomized controlled trial at an earlier stage is needed	[147]
Curosurf®	N/A	N/A	Surfactant therapy may be a useful intervention for severe MAS Randomized controlled clinical trials are needed	[148]
Survanta®	ETT instillation	Yes	Effective therapy, if started within 6 h after birth	[149]
Saline lavage in large volume (FRC-like) followed by Alveofact®	ETT instillation	HFOV	Interesting approach in the treatment of MAS	[150]
Survanta lavage	ETT instillation	Yes	An effective and safe method for treatment of severe MAS Multicenter randomized controlled trial is needed	[151]
Surfacten® lavage followed by surfactant replacement	ETT	Yes	Surfactant lavage an effective and safe method for treatment of severe MAS	[152]
Survanta lavage	ETT	Yes	Only a short-term effect in decreasing oxygenation index in neonates with MAS	[153]
Surfaxin® lavage	ETT	Yes	Safe and potentially effective therapy	[154]
Three different none: 1: Control 2: BAL with diluted Survanta 3: Group 2 plus single dexamethasone dose (iv.)	ETT	Yes	Group 3 in the first hours of life may be an effective treatment for severe MAS	[155]
Survanta BAL	ETT	Yes	Beneficial effects on pulmonary mechanics persisted for at least 48 h after administration	[156]
Curosurf	ETT	Yes	The approach is worth considering when ECMO is unavailable for the treatment of severe MAS	[157]
Curosurf	ETT	Yes plus manual ventilation with 100% O_2 for 1–2 min after each instillation	Surfactant may have a role in the treatment of severe MAS in term and near-term infants	[158]
Survanta lavage	Catheter inserted down ETT	Yes after administration	A randomized controlled trial is needed	[159]
Survanta lavage	Instillation	HFOV after delivery	May improve the outcome in newborn infants with severe MAS Prior to lung lavage, stabilization and optimal support may prevent unexpected results during and after lavage	[160]

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
Two none followed by iNO: Survanta lavage Bolus surfactant	ETT	Yes after delivery	No advantage of surfactant lavage therapy over bolus surfactant treatment in infants with MAS complicated by PPHN	[161]

BAL: Bronchoalveolar lavage; ECMO: Extracorporeal membrane oxygenation; ETT: Endotracheal tube; FRC: Functional residual capacity; HFOV: High frequency oscillatory ventilation; iNO: Inhaled nitric oxide; iv.: Intravenous; MAS: Meconium aspiration syndrome; PPHN: Persistent pulmonary hypertension; RDS: Respiratory distress syndrome.

Table 5

Surfactant therapy for neonates with congenital diaphragmatic hernia.

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
Natural substance derived from minced bovine lung	ETT	Yes	Important improvement in oxygenation	[162]
Infasurf®	ETT	N/A	A randomized controlled trial is needed	[163]
Survanta®	ETT	Yes	Less improvement because of factors other than surfactant deficiency Multicenter randomized controlled trial is needed	[164]
Surfacten®	ETT	Yes	Pulmonary hypoplasia accompanying CDH Improved oxygenation but controlled trials are needed	[165]
Alveofact® + iNO + ECMO	ETT	HFOV	Good survival rate and good neurodevelopmental outcome at 1 year of age	[166]
Survanta Exosurf® Curosurf® Others	N/A	N/A	Meta-analysis study Lower survival rate in CDH preterm infants Surfactant replacement in CDH can be used only within a randomized clinical trial	[167]
N/A	N/A	N/A	Meta-analysis study No benefit for term infants with a prenatal diagnosis of isolated CDH	[168]

CDH: Congenital diaphragmatic hernia; ECMO: Extracorporeal membrane oxygenation ETT: Endotracheal tube; HFOV: High frequency oscillatory ventilation; iNO: Inhaled nitric oxide.

Table 6

Surfactant therapy for neonates with pulmonary hemorrhage.

Surfactant therapy	Delivery method	Mechanical ventilation	Notes	Ref.
Exosurf®	N/A	N/A	Meta-analysis study	[169]
BLES®	ETT	Yes	For infants with respiratory deterioration due to PH Useful adjunctive therapy in neonates with a clinically significant PH Randomized controlled trial is needed	[170]
BLES	N/A	N/A	This study focused on the outcomes of PH in VLBW neonates treated with surfactant PH increased risk of death and short term morbidity but not associated with increase long term morbidity	[171]
Surfactant-TA	ETT via catheter	N/A	For respiratory failure due to HPE Useful adjunctive therapy to prevent surfactant inhibition and normalize the respiratory status of infants with HPE Randomized controlled trial is needed	[172]
Curosurf®	Intubated	N/A	Meta-analysis study of prophylactic versus rescue trials For PIVH as increased risk for very premature neonates with RDS	[173]

ETT: Endotracheal tube; HPE: Hemorrhagic pulmonary edema; PH: Pulmonary hemorrhage; PIVH: Peri-intraventricular hemorrhage; RDS: Respiratory distress syndrome; VLBW: Very low birth weight.

Table 7

Surfactant replacement therapy for neonates with miscellaneous pulmonary diseases.

Surfactant type	Delivery method	Mechanical ventilation	Disease	Notes	Ref.
Infasurf®	ETT instillation	Yes	ALI	Acute improvement in oxygenation with lower mortality	[174]
Infasurf	Intratracheal instillation	Manual during delivery	AHRF	Improved oxygenation and permitted moderation of ventilator support Multicenter randomized controlled trial is needed	[175]
Infasurf	ETT	Manually ventilated	AHRF	Rapid improvement in oxygenation, earlier extubation, and decreased requirement for intensive care	[176]
BLES®	ETT	Yes	CLD	Useful adjunctive therapy in neonates with early chronic lung disease	[177]
Survanta®	Intratracheal instillation	Yes	CLD	Early postnatal instillation of budesonide using surfactant as vehicle significantly improved the combined outcome of death or CLD Multicenter randomized controlled trial is needed	[178]
Curosurf®	Intubation	IPPV	Severe RDS and CLD	Meta-analysis study of prophylactic versus rescue trials Prophylactic administration demonstrated significant advantages over rescue therapy	[134]

Surfactant type	Delivery method	Mechanical ventilation	Disease	Notes	Ref.
Surfaxin®	Catheter into ETT	Yes	BPD	Reduced the incidence of death or BPD to high-risk preterm infants after the first 48 h of life	[179]
Curosurf	Catheter into ETT	Manual and CPPV	SB	Manual ventilation during delivery then resumed CPPV Improved SB by restoring surfactant activity Larger controlled trial is needed	[180]
Curosurf	Catheter into ETT	Before and after delivery	Severe RSV	Improved gas exchange and respiratory mechanics and shortened MV and ICU stay in infants with RSV-induced respiratory failure	[181]
Curosurf, Survanta, Alveofact®	N/A	N/A	GBS Pneumonia	Surfactant therapy improved gas exchange in term and preterm neonates with GBS pneumonia	[182]
Curosurf then Survanta after detecting the infection	Intratracheal bolus	Yes	ARDS due to chlamydial pneumonia	Extensive further trials are needed to elucidate the efficacy and probable side effects of the treatment plan	[183]
Alveofact	ETT	Yes	Respiratory failure due to bacterial sepsis	Surfactant seems to play a role in the defense against bacteria	[184]
Survanta	ETT	Yes	Respiratory failure requiring ECMO	Multiple-dose surfactant improved pulmonary function, increased surfactant protein A content,	[185]

Surfactant type	Delivery method	Mechanical ventilation	Disease	Notes	Ref.
				reduced disease complications and decreased time on ECMO duration	
Survanta	ETT	Yes but manual during dose delivery	Respiratory failure requiring ECMO	Use of surfactant, particularly in the early phase of respiratory failure, significantly decreased the need for ECMO, without increasing the risk of complications	[186]
Survanta	ETT	Yes	Extremely premature infants	Infants born at or before 26 week of gestation Improves survival rates without increasing the proportion of impaired survivors	[187]
Treated cases: Survanta = 79% Exosurf = 21%	N/A	Yes	High-risk preterm neonates	Neonates weighing 601–1300 g at birth Decreased mortality	[188]
Human surfactant	N/A	N/A	Children born very preterm	Evaluate long-term effects of surfactant therapy Surfactant therapy reducing mechanical ventilation needs or extra oxygen after birth may reduce the severity of immaturity related bronchial obstruction in childhood	[189]
Survanta	ETT	Yes	Congenital PAP associated with SP-B deficiency	Surfactant replacement did not retain surfactant composition, activity or pulmonary	[190]

Surfactant type	Delivery method	Mechanical ventilation	Disease	Notes	Ref.
				vascular permeability	

AHRF: Acute hypoxemic respiratory failure; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; CLD: Chronic lung disease; CPPV: Continuous positive-pressure ventilation; ECMO: Extracorporeal membrane oxygenation; ETT: Endotracheal tube; GBS: Group B streptococcal infection; ICU: Intensive care unit; IPPV: Intermittent positive pressure ventilator; MV: Mechanical ventilation; PAP: Pulmonary alveolar proteinosis; RDS: Respiratory distress syndrome; RSV: Respiratory syncytial virus; SB: Severe bronchiolitis.

Table 8

Surfactant replacement therapy by aerosol delivery for various pulmonary disorders.

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
Synthetic DPPC	0.25%	Inhalation	0.25 μm	N/A	NRDS (infant)	Inconclusive results needing further study	[41]
Synthetic DPPC	1%	MHz ultrasonic generator	N/A	N/A	NRDS (infant)	The study estimated that 3 mg /kg DPPC could provide an alveolar monolayer	[61]
DPPC/DPPG (9:l)	N/A	Nebulizer	N/A	N/A	NRDS (infant)	An improvement in the level of PL but not a coincidental improvement in the disease	[42]
Pure DPPC and PG	25 mg powder in capsule	Modified bag [†]	100 μm	N/A	NRDS (infant)	Surfactant dry powder blow down ETT Substantially less improvement compared with that attained with animal or human surfactant	[44]
[^{3}H] Survanta®	Approximately 875 mg PL (Tot Lav-Neb)[‡]	Actuated nebulizer	MMAD = 2–3 μm GSD = 1.9–2.1	105 ± 7 mg PL (Tot Lav-Neb)	ARDS with pattern of ALI (adult sheep)	No major changes in ventilation-perfusion matching as measured at the lobar level Underlying pattern of ALI affected surfactant distribution and hence, physiologic responses to the surfactant therapy More aerosolized surfactant deposited in the injured lung improved physiologic response	[62]
[^{3}H] Survanta	Approximately 800 mg PL (Par Lav-Neb)[§]	Actuated nebulizer	MMAD = 2–3 μm GSD = 1.9–2.1	79 ± 7 mg PL (Par Lav-Neb)	ARDS with pattern of ALI (adult sheep)	No major changes in ventilation-perfusion matching as measured at the lobar level Underlying pattern of ALI affected	[62]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
						surfactant distribution and hence, physiologic responses to the surfactant therapy More aerosolized surfactant deposited in the injured lung improved physiologic response	
Exosurf®	240 ml of 13.5 mg/ml PL	Visan-9 nebulizer	N/A	>5 mg the dose of 112 mg PL/kg/day	Sepsis induced ARDS (adult)	No improvement in oxygenation, peak airway pressure, or overall survival at 30 days No reduction in the time required for MV, the need for oxygen supplementation, or the length of the stay in the ICU or the hospital	[100]
Surfactant from fresh sheep lung	10 ml of 15 mg/ml surfactant	Ultrasonic nebulizer	MMD = 0.44 μm and initial particle diameter = 2.40 μm	N/A	Preterm neonatal rabbit	An initial oropharyngeal dose of surfactant (50 μl of 30 mg/ml PL) was given A dried, hygroscopic aerosol is an effective means of surfactant delivery to spontaneously breathing premature rabbit neonates	[11]
[^{99m}Tc] Alveofact®	2 ml of of 45 mg/ml surfactant	Three jet nebulizers	70% = 1–5 μm[¶]	10% for MiniNEB & 1–3% for Intersurgical and Flo-Thru nebulizers	Lung-lavaged rabbit	No change in surfactant composition and biophysical properties by nebulization Low nebulization efficiency as most surfactant aerosol is deposited in the expiratory tubing The particle size distribution of the surfactant aerosol as produced by MiniNEB ensures a peripheral	[106]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
						deposition in the lungs Nebulization is feasible, but improving the efficiency of the procedure is needed	
Alveofact	2.4 ml of 120 mg surfactant	Jet nebulizer	75% <5μm[#] MMAD = 3.4 μm GSD = 1.7	N/A	CF (adult)	No significant acute or short-term effect Insufficient quantity delivered, non-uniform distribution or inhibition of the surfactant in the lungs may be reasons for a lack of effect	[110]
Curosurf®	480 mg	A modified Aiolos® nebulizer + CPAP support	N/A	N/A	NRDS (infant)	No beneficial effects of aerosolized surfactant contrary to data from animal experiments Selective deposition of highly surfactant aggregates from the aerosol, or better surfactant distribution may be reasons	[56]
Surfaxin®	72 mg PL over 3 h	Vibrating mesh nebulizer + CPAP	MMAD = 1.9 ± 0.3 μm	N/A	NRDS (infant)	Safe and well tolerated Lack of efficiency as there was no control group included	[102]

ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; CF: Cystic fibrosis; CPAP: Continuous positive airway pressure; DPPC: Dipalmitoylphosphatidylcholine; DPPG: Dipalmitoylphosphatidylglycerol; ETT: Endotracheal tube; GSD: Geometric standard deviation; ICU; Intensive care unit; MMAD: Mass median aerodynamic diameter; MV: Mechanical ventilation; NRDS: Neonates with respiratory distress syndrome; PG: Phosphatidylglycerol; PL: Phospholipids.

[†]Modified bag: Modified Laerdal neonatal resuscitation bag with attachment to hold capsule size 2 of artificial surfactant.

[‡]Tot Lav-Neb: Total lung lavage group treated with 32 ± 2 ml nebulized surfactant.

[§]Par Lav-Neb: Partial lung lavage group treated with 35 ± 2 ml nebulized surfactant.

[¶]70% = 1–5 μm: 70% of the particle have particle diameter ranged from of 1–5 μm.

[#]75% <5μm: 75% of the particle have particle diameter less than of <5μm.

Table 9

Comparison studies of surfactant delivery by nebulization and instillation in animal models.

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
[^{3}H] NS [^{3}H] Survanta® 308 mg NS 248 mg Survanta	Actuated nebulizer + MV	MMAD = 1.8–2.3 μm, GSD = ±2.1	5.4 mg NS 6.7 mg Survanta	NRDS (lamb fetuses)	Compare between surfactant delivery methods and between surfactant types More surfactant deposition in the right upper lobes and tracheae in the nebulized none compared with the instilled group Aerosolized surfactant improved lung function at a very low surfactant dose	[92]
[^{3}H] NS [^{3}H] Survanta 50 mg NS/kg	ETT + MV before and after delivery	N/A	96.7% NS	NRDS (lamb fetuses)	Compare between surfactant delivery methods and between surfactant types More surfactant deposition in the right upper lobes and tracheae in the nebulized none compared with the instilled group Aerosolized surfactant improved lung function at a very low surfactant dose	[92]
[^{3}H] Survanta 20 mg PL/ml (12.3 ml)	A low-flow nebulizer	MMAD = 1.6 μm, GSD = 2	9.1 ± 1.7 mg PL (3.6% of 12.3 ml)	Severe lung injury (rabbit)	Surfactant aerosol resulted in modest physiological improvements in lung injury model and was superior to the tracheal instillation technique	[40]
[^{3}H] Survanta 20 mg PL/ml (5 ml/kg)	ETT + MV	N/A	N/A	Severe lung injury (rabbit)	Surfactant aerosol resulted in modest physiological improvements in lung injury model and was superior to the tracheal	[40]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
						instillation technique	
[^{3}H] Survanta	528 ± 61 mg (21.1 ml)	A low-flow nebulizer	MMAD = 2–3 μm, GSD = 1.9-2.1	168 ± 27 mg	Non-uniform pattern of lung injury (adult sheep)	Various delivery techniques led to significant difference in distribution patterns Surfactant aerosol was poorly deposited in the severely injured regions, reflecting poor ventilation of these regions Surfactant aerosol had greater improvements in oxygenation and ventilator parameters compared with tracheal instilled animals	[49]
[^{3}H] Survanta	4000 ± 132 mg (160 ml)	ETT	N/A	2525 ± 251 mg	Non-uniform pattern of lung injury (adult sheep)	Various delivery techniques led to significant difference in distribution patterns Surfactant aerosol was poorly deposited in the severely injured regions, reflecting poor ventilation of these regions Surfactant aerosol had greater improvements in oxygenation and ventilator parameters compared with tracheal instilled animals	[49]
[^{3}H] Survanta	304 ± 50 mg (12 ml)	Actuated nebulizer	MMAD = 2.2–2.8 μm, GSD = 1.9–2.1	6.1 ± 2.2% in the peripheral lung tissue	ALI (adult sheep)	Improved lung function with notably different amount of surfactant deposited in lung tissue for the two delivery methods	[50]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
						Instillation was superior to aerosolization Superior distribution pattern within the lungs of aerosolized surfactant compared with instilled surfactant	
[^{3}H] Survanta	3410 ± 130 mg	ETT	N/A	51%	ALI (adult sheep)	Improved lung function with notably different amount of surfactant deposited in lung tissue for the two delivery methods Instillation was superior to aerosolization Superior distribution pattern within the lungs of aerosolized surfactant compared with instilled surfactant	[50]
[^{125}I] Sheep NS	25 mg PL/ml	Ultrasonic nebulized (Neb)	MAD = ~3 μm	23.4 ± 2.5%	Lamb fetuses	The potential for nebulized surfactant therapy in RDS may be limited by the non-homogeneous nature of ventilation in the preterm lung	[94]
[^{125}I] Sheep NS	25 mg PL/ml	Inst/Inst†	N/A	75 ± 1%	Lamb fetuses	The potential for nebulized surfactant therapy in RDS may be limited by the non-homogeneous nature of ventilation in the preterm lung	[94]
[^{125}I] Sheep NS	25 mg PL/ml	Inst/Neb‡	N/A	23.4 ± 2.5%	Lamb fetuses	The potential for nebulized surfactant therapy in RDS may be limited by the non-homogeneous nature of ventilation in	[94]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
						the preterm lung	
[^{99m}Tc] Alveofact®	100 mg/kg	MiniNEB nebulizer	MMAD = 3 μm and 70% of particles = 1–5 μm.	N/A	RDS (rabbit)	Instillation was followed by a rapid decrease in MABP and a more marked drop in cerebral blood flow, while during nebulization, MABP did not alter and cerebral blood flow decreased less and more gradually	[109]
[^{99m}Tc] Alveofact	100 mg/kg	ETT	N/A	N/A	RDS (rabbit)	Instillation was followed by a rapid decrease in MABP and a more marked drop in cerebral blood flow, while during nebulization, MABP did not alter and cerebral blood flow decreased less and more gradually	[109]
Alveofact	8.83 ± 0.69 ml of 10 mg/ml	Ultrasonic nebulized	MMAD = 4.5 μm GSD = 2.6	20.4 ± 1.5 mg	ALI (isolated rabbit lungs)	Nebulizers used for efficient delivery of surfactant to the distal bronchoalveolar space Low amounts of inhaled surfactant may be more effective in improving gas exchange than large amounts of instilled substance	[27]
Alveofact	30 mg	ETT	N/A	30.0 ± 0.0 mg	ALI (isolated rabbit lungs)	Nebulizers used for efficient delivery of surfactant to the distal bronchoalveolar space Low amounts of inhaled surfactant may be more effective in improving gas exchange than large amounts of instilled substance	[27]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
[^{99m}Tc] Alveofact	100 mg/kg (1.8 ± 0.1 kg)	Miniheart low-flow nebulizer + HFV	MMAD = 3 μm and 70% of particles = 1–5 μm.	9.8%	RDS (rabbit)	Aerosols during HFV improved lung function at low alveolar dose without improving distribution, with less effect on blood pressure and cerebral blood flow compared with surfactant instillation Both modes of surfactant treatment led to non-uniform distribution with less uniform distribution after nebulization	[2]
[^{99m}Tc] Alveofact	100 mg/kg (1.8 ± 0.1 kg)	Instillation as a bolus injection + HFV	N/A	91%	RDS (rabbit)	Aerosols during HFV improved lung function at low alveolar dose without improving distribution, with less effect on blood pressure and cerebral blood flow compared with surfactant instillation Both modes of surfactant treatment led to non-uniform distribution with less uniform distribution after nebulization	[2]
Alveofact	36.4 mg/kg	Ultrasonic nebulized	MMAD = 4.5 μm and GSD = 2.3	8.6 mg/kg	ALI (rabbit lungs: 2.5–3.1 kg)	Low doses of aerosols are similarly effective as normal doses of instilled surfactant in reducing shunt flow in ALI model, but apply more beneficial effects on ventilation perfusion matching	[101]
Alveofact	80 mg/kg	ETT	N/A	N/A	ALI (rabbit lungs: 2.5–3.1 kg)	Low doses of aerosols are similarly effective as normal doses of	[101]

Surfactant	Dose delivered	Delivery method	Aerosol particle size	Amount deposited	Disease (model)	Notes	Ref.
						instilled surfactant in reducing shunt flow in ALI model, but apply more beneficial effects on ventilation perfusion matching	
Porcine surfactant	800 mg/kg	Nebulizer	≥2.0 μm	25 mg/kg	OA induce ALI (rat: 0.2–0.25 kg)	Aerosolized surfactant inhaled by spontaneous breathing may effectively reduce severe lung injury It is simple, safe and combines the therapeutic effects of a surfactant with partial oxygen inhalation under spontaneous breathing	[12]
Porcine surfactant	100 mg/kg	ETT	N/A	N/A	OA induce ALI (rat: 0.2–0.25 kg)	Aerosolized surfactant inhaled by spontaneous breathing may effectively reduce severe lung injury. It is simple, safe and combines the therapeutic effects of a surfactant with partial oxygen inhalation under spontaneous breathing	[12]

ALI: Acute lung injury; ETT: Endotracheal tube; GSD: Geometric standard deviation; HFV: High frequency ventilator; MABP: Mean arterial blood pressure; MMAD: Mass median aerodynamic diameter; MV: Mechanical ventilation: Neb: Nebulized surfactant; NS: Natural surfactant; NRDS: Neonates with respiratory distress syndrome; OA: Oleic acid; PL: Phospholipids; RDS: Respiratory distress syndrome.

† Inst/Inst: Animals received instilled surfactant followed by a second instilled dose.

‡ Inst/Neb: Animals received instilled surfactant followed by a nebulized surfactant.