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Surfactant for Pediatric Acute Lung Injury

Douglas F. Willson, MD[a], **Patricia R. Chess, MD**[b], and **Robert H. Notter, MD, PhD**[c]

[a]Professor of Pediatrics and Medical Director, PICU and Division of Pediatric Critical Care, University of Virginia, Charlottesville, VA

[b]Associate Professor of Pediatrics and Biomedical Engineering, University of Rochester School of Medicine, Rochester, NY

[c]Professor of Pediatrics and Environmental Medicine, University of Rochester, Rochester, NY

Synopsis

This article reviews exogenous surfactant therapy and its use in mitigating acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) in infants, children, and adults. Biophysical and animal research documenting surfactant dysfunction in ALI/ARDS is described, and the scientific rationale for treatment with exogenous surfactant is discussed. Major emphasis is on reviewing clinical studies of surfactant therapy in pediatric and adult patients with ALI/ARDS. Particular advantages from surfactant therapy in direct pulmonary forms of these syndromes are described. Also discussed are additional factors affecting the efficacy of exogenous surfactants in ALI/ARDS, including the multifaceted pathology of inflammatory lung injury, the effectiveness of surfactant delivery in injured lungs, and composition-based activity differences among clinical exogenous surfactant preparations.

I. Introduction

Because of their extensive alveolar network and capillary vasculature, the lungs have significant exposure and susceptibility to injury from toxins and pathogens present either in the circulation or in the external environment. The medical consequences of acute pulmonary injury in pediatric and adult patients are frequently defined as the syndromes of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The American-European Consensus Conference in 1994 defined ALI as respiratory failure of acute onset with a PaO_2/FiO_2 ratio ≤300 mmHg (regardless of the level of positive end expiratory pressure, PEEP), bilateral infiltrates on frontal chest radiograph, and a pulmonary capillary

Corresponding author for proofs and reprints: Douglas F. Willson, MD, Division of Pediatric Critical Care, University of Virginia Children's Medical Center, UVA Health Sciences System, Box 800386, Charlottesville, VA 22908-0386, Phone: 434-982-1707, Fax: 434-982-3843, Email: dfw4m@virginia.edu.
Coauthors' addresses: Patricia R. Chess, MD, Robert H. Notter, MD, PhD, Department of Pediatrics, Box 651 (Chess); Box 850 (Notter), University of Rochester Sch of Med, 601 Elmwood Avenue, Rochester, NY 14642, Phone: 585-275-5948, Patricia_Chess@urmc.rochester.edu, Robert_Notter@urmc.rochester.edu

wedge pressure <18 mmHg (if measured) or no evidence of left atrial hypertension [1]. ARDS is defined identically except for a lower PaO_2/FiO_2 limit of <200 mmHg [1]. The Consensus Committee definitions of ALI/ARDS are widely-used clinically, supplemented by lung injury or critical care scores such as the Murray [2] or APACHE II [3] scores in adults, or the PRISM [4, 5], PIM [6], or Oxygenation Index [7] in children.

The incidence of ALI/ARDS has been variably reported to be 50,000–190,000 cases per year in the United States [1, 8–14]. The incidence of ALI in two recent studies has been estimated at 22–86 cases per 100,000 persons per year [13, 14], with 40–43 percent of these patients having ARDS [13]. These studies primarily considered adults; the incidence of ALI/ARDS has been reported to be significantly lower at 2–8 cases per 100,000 persons per year in the pediatric age group (e.g., [15–19]). Survival statistics for patients with ALI/ARDS vary depending on specific lung injury etiology and age, but overall mortality rates in both adult and pediatric patients remain very substantial despite sophisticated intensive care [1, 8–14, 16–19]. Mortality rates reported in a series of studies in pediatric patients with ALI/ARDS are given in Table 1 [15, 19–25]. The significance of distinguishing between the two clinical syndromes in a practical sense is uncertain, since a meta-analysis of 102 studies prior to 1996 suggested little or no difference in mortality rates between patients meeting criteria for ALI compared to ARDS [9]. This was also the conclusion in the recent NEJM article by Rubenfeld et al [13], which reported mortality rates of 38.5% for ALI and 41% for ARDS, with an estimated 74,500 deaths per year and an aggregate 3.6 million hospital days of care in the United States.

There is clearly a significant need for improved treatments for ALI/ARDS in all age groups, and this review focuses on the potential utility of exogenous surfactant replacement therapy. Although the clinical syndromes of ALI and ARDS encompass a broad spectrum of etiologies, it is important to consider specific etiologies in targeting surfactant therapy. In particular, it is important to distinguish between ALI/ARDS from direct pulmonary causes as opposed to systemic (indirect, non-pulmonary) causes. Direct pulmonary causes of ALI/ARDS include lung viral or bacterial infections, gastric aspiration, blunt thoracic trauma with lung contusion, meconium aspiration (infants), near-drowning, thoracic radiation, hyperoxia, and the inhalation of smoke or other toxicants. Indirect (systemic) causes of ALI/ARDS include sepsis, closed space burn injury, hypovolemic shock, non-thoracic trauma, multiple transfusions, and pancreatitis. The pathology of ALI/ARDS is particularly complex in indirect insults like sepsis, where multi-organ involvement is common and extra-pulmonary inflammation is severe and pervasive. The multifaceted systemic pathology of ALI/ARDS from non-pulmonary causes of lung injury likely renders therapy with exogenous surfactant less effective compared to direct pulmonary ALI/ARDS. As detailed later, post-hoc analyses in two recent clinical trials of surfactant therapy in ALI/ARDS suggest greater efficacy in direct as opposed to indirect pulmonary injury [25, 26]. In all forms of ALI/ARDS, the major rationale for surfactant therapy is the presence of surfactant dysfunction in the injured lungs (Figure 1). Although ALI/ARDS can include chronic lung injury in its later fibro-proliferative phase, surfactant dysfunction is most prominent in the acute phase of ALI/ARDS as described below.

II. Surfactant dysfunction in acute pulmonary injury

Total lavaged phospholipid is either unchanged or increased in most animal models of ALI/ARDS, including models of direct pulmonary injury such as gastric aspiration or respiratory infection [27–32]. Although surfactant deficiency can potentially occur during the course of ALI/ARDS (e.g., from type II cell injury), surfactant dysfunction in association with inflammation and permeability injury is generally much more prominent. Impairments in lung surfactant activity, and reductions in the content or composition of active large surfactant aggregates, have been reported in BAL, edema fluid, or tracheal aspirates from patients with ALI/ARDS or other diseases involving lung injury [33–45]. Research over the last two decades has identified a number of pathways and mechanisms contributing to surfactant dysfunction in acute pulmonary injury as summarized below (for review see [27, 46, 47]):

One prevalent pathway of surfactant dysfunction in lung injury is through biophysical or chemical interactions with substances present in the alveoli as a result of permeability edema or inflammation. Biophysical studies *in vitro* have shown that the surface activity of lung surfactant can be impaired by multiple injury-related inhibitors including plasma and blood proteins [48–55], meconium [56], cell membrane lipids [50, 55, 57], fluid free fatty acids [55, 58–60], reactive oxidants [58, 61–63], and lytic enzymes including proteases [64] and phospholipases [65, 66]. Surfactant dysfunction associated with inhibitory substances in the lungs has also been widely-demonstrated in animal models of acute inflammatory lung injury [27–32, 46, 67–69]. In terms of physicochemical mechanisms of action, albumin and other blood proteins impair the surface activity of lung surfactant primarily by competitive adsorption that reduces the entry of active surfactant components into the air-water interface [52, 70]. In contrast, cell membrane lipids, lyso-phospholipids, or fatty acids act at least in part by mixing into the surface film and compromising its ability to reach low surface tension during dynamic compression [50, 55, 59, 70]. Also, phospholipases, proteases, and reactive oxygen-nitrogen species can act to chemically degrade or alter functionally-essential surfactant lipids or proteins [64, 66, 71]. It is well-documented that surfactant activity deficits from these various mechanisms can be overcome or at least mitigated *in vitro* by increasing the concentration of active surfactant even if inhibitor substances are still present [27, 46, 47].

Another pathway by which surfactant activity can be reduced during lung injury is by depletion or alteration of active large aggregates. Surfactant exists in the alveolar hypophase in a size-distributed microstructure of aggregates, the largest of which typically have the greatest surface activity and the highest apoprotein content [60, 72–78]. The percentage of large aggregates and their content of SP-A and SP-B are reduced in bronchoalveolar lavage from patients with ARDS [38–40]. Animal studies of ALI/ARDS indicate that large surfactant aggregates can be depleted or reduced in activity by molecular interactions with inhibitor substances as well as by changes in surfactant aggregate metabolism in the alveoli or involving altered reuptake or recycling in type II cells [30, 60, 79–81]. Although large aggregates are depleted or compromised in many forms of ALI/ARDS, information on total surfactant pools is inconsistent, with both decreased [35, 37] and unchanged amounts [34, 36] reported.

The ability of exogenous surfactant therapy to reverse or mitigate acute respiratory pathology in animal models of ALI/ARDS has also been extensively documented (Table 2). Examples of animal studies showing benefits to acute lung function or mechanics following surfactant therapy include acid aspiration [82–84], meconium aspiration [85–88], anti-lung serum [89], bacterial or endotoxin injury [90–95], bilateral vagotomy [96], hyperoxia [97–101], *in vivo* lavage [102–107], N-nitroso-N-methylurethane (NNNMU) injury [108–110], and viral pneumonia [111, 112]. These acute animal model studies typically did not address long-term outcomes. However, significant improvements in respiratory function would be expected to lead to improved long term outcomes in patients with ALI/ARDS, provided that untreated elements of pathology do not blunt this effect. As noted earlier, this is most likely to be the case in direct pulmonary forms of ALI/ARDS.

III. Clinical exogenous surfactant drugs

Although endogenous surfactant contains similar chemical constituents across mammalian species, this is not true of exogenous surfactant drugs. The degree of resemblance of pharmaceutical surfactants to native surfactant is highly variable, and has direct consequences for surface and physiological activity. Pharmaceutical surfactants comprise three functionally-relevant classifications (Table 3): (I) organic solvent extracts of lavaged lung surfactant from animals; (II) organic solvent extracts of processed animal lung tissue with or without additional synthetic additives; and (III) synthetic preparations formulated *in vitro* without material from animal lungs. Organic solvent extracts of lavaged alveolar surfactant (Category I) contain all of the hydrophobic lipid and protein components of endogenous surfactant, although specific compositional details can vary depending on preparative methodology. Extracts of minced or homogenized lung tissue (Category II) necessarily contain some non-surfactant components, and require more extensive processing that can further alter composition compared to native surfactant. The synthetic surfactants in Category III that have been most widely studied are Exosurf® and ALEC® (artificial lung expanding compound), although neither of these two preparations is in active clinical use because they have been shown to have inferior activity compared to animal-derived surfactants (e.g., [46, 51, 113–117]). Two additional synthetic surfactants, KL4 (Surfaxin®) and recombinant SP-C surfactant (Venticute®), are presently undergoing clinical evaluation, and new synthetic lipid:peptide exogenous surfactants are currently under development.

Four exogenous surfactant preparations are currently licensed for clinical use in RDS in the United States: Infasurf®, Survanta®, Curosurf®, and Exosurf® (the latter is no longer used as noted above). As reviewed elsewhere [46, 118, 119], Infasurf® is a direct chloroform:methanol extract of large aggregate surfactant obtained by bronchoalveolar lavage from calf lungs. Survanta® is an extract of minced bovine lung tissue to which is added synthetic dipalmitoyl phosphatidylcholine (DPPC), tripalmitin, and palmitic acid. Curosurf® is prepared from minced porcine lung tissue by a combination of washing, chloroform-methanol extraction, and liquid-gel chromatography. In addition, Surfaxin® (KL4 surfactant), which is under consideration for FDA-approval, is made up of a 21 amino acid peptide that has repeating units of one leucine (K) and four lysine (L) residues and is combined at 3% by weight with a 3:1 mixture of DPPC and palmitoyl-oleoyl phosphatidylglycerol plus 15% palmitic acid. The synthetic surfactant Venticute®, which

has also been studied in ARDS as noted later, contains synthetic lipids and palmitic acid plus a 34 AA modified human recombinant SP-C that has substitutions of phenylalanine for cysteine at two positions and isoleucine for methionine at another [46].

IV. Current studies on surfactant replacement therapy in patients with ALI/ARDS

A significant number of clinical studies have reported benefits following the instillation of exogenous surfactants to term infants, children, or adults with ALI/ARDS or related acute respiratory failure [25, 120–135] (Table 4). However, many of these are small case series or pilot studies, and found only improvements in acute lung function (oxygenation). Controlled trials of surfactant therapy in patients with ALI/ARDS have met with mixed success, particularly in adults with sepsis-associated ARDS [136, 137]. A summary of the clinical experience with exogenous surfactant therapy in term infants, children and adults is given below.

The best-studied application of surfactant therapy in term infants with acute pulmonary injury is in meconium aspiration syndrome [129–133]. Meconium obstructs and injures the lungs when aspirated and is known to cause surfactant dysfunction [56, 138]. Auten et al [129], Khammash et al [132], and Findlay et al [133] have all reported significant improvement from surfactant administration in infants with meconium aspiration. The randomized controlled study of Findlay et al [133] found reductions in the incidence of pneumothorax, duration of mechanical ventilation and oxygen therapy, time of hospitalization, and requirements for ECMO in 20 term infants treated with Survanta® compared to controls. Lotze et al [130, 131] also reported favorable results using Survanta® in a controlled trial in term infants referred for ECMO due to severe respiratory failure (meconium aspiration was a prevalent diagnosis in both studies). Twenty-eight infants treated with four doses of Survanta® (150 mg/kg) had improved pulmonary mechanics, decreased duration of ECMO treatment, and a lower incidence of complications after ECMO compared to control infants [130]. A subsequent multicenter controlled trial in 328 term infants also reported significant improvements in respiratory status and the need for ECMO following surfactant treatment [131]. Surfactant therapy has also been found to be beneficial to lung function or respiratory outcome in several studies in infants with viral respiratory (RSV) infection [134, 135, 139]. Luchetti et al [134] reported that 10 infants with RSV-bronchiolitis treated with tracheally-instilled porcine-derived surfactant (Curosurf®, 50 mg/kg body weight) had improved gas exchange and a reduced time on mechanical ventilation and in the pediatric intensive care unit compared to an equal number of control infants not treated with exogenous surfactant. A subsequent multicenter controlled trial in 40 patients also found that surfactant therapy with Curosurf® improved gas exchange and respiratory mechanics, and shortened the duration of mechanical ventilation and hospitalization, in infants with acute respiratory failure from RSV bronchiolitis [135]. Also, Tibby et al [139] have reported that 9 infants with severe RSV bronchiolitis who received two doses of Survanta® (100 mg/kg) had a more rapid improvement in oxygenation and ventilation indices in the first 60 hours compared to 10 control infants receiving air-placebo. Exogenous surfactant therapy is now used in neonatal intensive care units at many

institutions to treat respiratory failure in term infants with meconium aspiration or pulmonary viral/bacterial infection. Surfactant therapy has also been studied in infants with congenital diaphragmatic hernia, but its use remains controversial in this context [140, 141].

Studies of surfactant therapy in children and adults with ALI/ARDS show positive results in a number of case reports or relatively small pilot trials [120, 121, 124–128]. However, particularly in adults, controlled clinical trials have been less successful. By far the largest prospective controlled study of surfactant therapy in adults with ARDS was definitively negative [136]. Anzueto et al [136] administered nebulized Exosurf® vs. placebo to 725 adults with ARDS secondary to sepsis and found no improvement in any measure of oxygenation and no effect on morbidity or mortality. However, interpretation of these negative results is confounded because both laboratory and clinical studies have documented that Exosurf® has low activity compared to animal-derived surfactants [51, 113–117, 142–145], and aerosolization has not been shown to be as effective as airway instillation in delivering surfactant. Gregory et al [137] reported small benefits in oxygenation in a controlled trial in adults with ARDS who received four 100 mg/kg doses of Survanta®, but with no overall advantage in survival in the 43 surfactant-treated patients studied. A more recent study by Spragg et al [26] using recombinant SP-C surfactant (Venticute®) in adults with ARDS showed immediate improvements in oxygenation, but no longer-term improvement in duration of mechanical ventilation, lengths of stay, or mortality. Post-hoc analysis did suggest, however, that the response in the subgroup of patients with ARDS due to “direct lung injury” was positive, and a follow-up prospective study in this group of patients is currently underway.

Controlled studies of surfactant therapy in children up to age 21 with ALI/ARDS have been more encouraging. A randomized but unblinded controlled trial by Willson et al [125] in 42 children at eight centers with ALI/ARDS showed that those receiving Infasurf® (70 mg/kg) had immediate improvement in oxygenation and fewer ventilator days and days in intensive care (Figure 2). This unblinded trial followed an initial open-label study by the same group demonstrating improved oxygenation in 29 children (0.1–16 yrs) treated with instilled Infasurf® [124]. In addition, a clinical trial by Moller et al [146] reported that children with ARDS showed an immediate improvement in oxygenation and less need for rescue therapy following treatment with Survanta®, although this latter study was underpowered for more definitive outcomes. Most recently, a large blinded, randomized, controlled study by Willson et al [25] in 152 pediatric patients with ALI/ARDS (77 surfactant treated and 75 placebo) yielded very positive results, showing both immediate improvements in oxygenation as well as a significant survival advantage for patients receiving calfactant (Infasurf®) relative to placebo (Table 5). Patients aged 1 wk through 21 years in this 21 center study were enrolled within 48 hr of endotracheal intubation with radiographic evidence of bilateral lung disease and an oxygenation index greater than 7. Patients with pre-existing lung, cardiac, or central nervous system were excluded. Ventilator-free days and mortality were primary outcomes. Surfactant treatment resulted in decreased oxygenation index, decreased mortality, and a higher percentage of response to conventional mechanical ventilation compared to air-placebo (Table 5). A post-hoc analysis indicated that the great majority of these beneficial effects were confined to patients with direct injury forms of ALI/ARDS (Table 6).

None of the above studies in infants, children, or adults showed any significant adverse long-term effects from surfactant administration, although transient hypoxia and some hemodynamic instability surrounding intratracheal or bronchoscopic instillation appear common. Transmission of infectious agents or allergic reactions has also not been reported with any of the exogenous surfactants currently licensed in the United States.

V. Considerations affecting the efficacy of exogenous surfactant therapy in ALI/ARDS

Several factors increase the difficulty of developing effective surfactant therapy for ALI/ARDS. As emphasized earlier, patients with ALI/ARDS share aspects of lung injury pathophysiology, but these diagnoses are clinical syndromes that comprise a diverse set of etiologies. The occurrence of ALI/ARDS in a heterogeneous population of patients with varying degrees of lung injury and systemic disease significantly reduces the resolving power of clinical trials of surfactant therapy. In addition, edema and inflammation in patients with acute pulmonary injury make it more difficult to deliver and distribute exogenous surfactant to the alveoli. Finally, meaningful evaluations of surfactant therapy in ALI/ARDS must account for differences in surfactant drug activity that can significantly impact therapeutic efficacy. Specific considerations for surfactant therapy in ALI/ARDS are discussed below.

Delivery methods and dosages for exogenous surfactant therapy in patients with lung injury

The primary method used to deliver exogenous surfactants to children and adults with ALI/ARDS is based on that shown to be most effective in premature infants with RDS, i.e., direct intratracheal instillation through an endotracheal tube or airway instillation through a bronchoscope. Surface active material instilled into the airways has the capacity to rapidly spread and distribute to the periphery of the lung [147–149]. Spreading from the central airways towards the alveoli is promoted by surface tension gradients that drive transport from regions of high surfactant concentration to regions of lower surfactant concentration. Typical doses of intratracheal surfactant in premature infants are 100 mg/kg body weight. This represents a significant excess over the amount of surfactant phospholipid needed to cover the surface of the alveolar network with a tightly packed surfactant film (only about 3 mg/kg of surfactant phospholipid at a molecular weight of 750 Daltons are needed to form a monomolecular film at a limiting area of 40 $Å_2$/molecule over an alveolar surface of 1 m^2/kg body weight [46, 150]). Excess instilled exogenous surfactant that reaches the alveoli provides a reservoir of material for the hypophase and interface, and is available for incorporation into endogenous surfactant pools via recycling pathways.

Although instillation is an effective method of delivering exogenous surfactants, total dosages required in older children and adults with ALI/ARDS are non-trivial. To achieve a comparable dose to that of premature infants based on body weight or body surface area, much larger total drug amounts and volumes are required. The prototypical “70 kg adult” requires 7 grams of exogenous surfactant at a dosage level of 100 mg/kg body weight. This necessitates an instilled volume of 87.5–280 ml at the phospholipid concentrations of current

clinical surfactant drugs in saline (25–80 mg/ml). It is obviously important to minimize instilled surfactant volumes in patients with severe respiratory failure as in ALI/ARDS. At the same time, instilled surfactant volume impacts intrapulmonary drug distribution, which is already compromised by edema and inflammation as noted earlier. Studies in animal models of ALI/ARDS have indicated that the distribution of exogenous surfactant can be improved by instilling larger fluid volumes or utilizing associated bronchoalveolar lavage [151–154], but the feasibility and/or utility of these approaches in clinical practice is uncertain. Clinical studies on intratracheal or bronchoscopic instillation of exogenous surfactants in patients with ALI/ARDS have used a range of instilled volumes, with doses as high as 300 mg/kg [155] and as low as 25 mg/kg [26].

An alternative to administering exogenous surfactant drugs by instillation is to deliver them in aerosol form. In theory, aerosolization could significantly reduce required surfactant doses, since delivery can be targeted to the alveoli by controlling particle size. Phospholipid aerosols with stable particle sizes appropriate for alveolar deposition in normal lungs can be formed by ultrasonic or jet nebulization [150, 156, 157], and exogenous surfactants have been aerosolized to animals and patients with surfactant deficiency or dysfunction [91, 105, 110, 136, 158–160]. However, the theoretical potential of aerosols to improve alveolar deposition and reduce required surfactant doses has not been replicated in practice. Aerosol methodology to date has not been shown to deliver exogenous surfactants to the alveoli as effectively as instillation, although this may improve in the future as technology advances.

Another approach to facilitate the delivery and distribution of exogenous surfactants in injured lungs involves the use of specific modes and strategies of mechanical ventilation. For example, studies indicate that the distribution and/or efficacy of instilled exogenous surfactant can be improved by jet ventilation [161, 162] and partial liquid ventilation [163–165]. Additional mechanism-based research on the impact of specific ventilation methods and strategies on the delivery, distribution, and efficacy of exogenous surfactants may be important for optimizing this therapy in ALI/ARDS. The delivery and distribution of surfactant drugs in injured lungs could also potentially be improved by the use of low viscosity formulations to reduce transport resistance after tracheal or bronchoscopic instillation. Whole surfactant and animal-derived exogenous surfactants have complex non-Newtonian, concentration-dependent viscosities that vary significantly among preparations [166, 167]. For a given surfactant preparation at fixed shear rate, viscosity can be significantly reduced by altering the physical formulation through changes in dispersion methodology, ionic environment, or temperature [166, 167].

Activity and inhibition resistance of exogenous surfactant drugs

One of the most important considerations in the clinical efficacy of surfactant therapy is the relative activity of different exogenous surfactant drugs. Differences in efficacy between clinical exogenous surfactants have been demonstrated in a number of comparison trials in premature infants [114–117, 142–145, 168, 169]. Results of these clinical comparisons indicate that “natural” surfactants derived from animal lungs (Categories I and II in Table 3) have significantly greater efficacy than the protein-free synthetic surfactants Exosurf® and ALEC. This is also the conclusion of retrospective meta analyses combining clinical data

from multiple surfactant trials [170–174]. As noted earlier, the largest study of surfactant therapy in adults with ALI/ARDS utilized the protein-free synthetic surfactant Exosurf® and found no therapeutic benefit [136]. The hydrophobic surfactant proteins are highly-active in endogenous surfactant, and substituting for them effectively in protein-free synthetic surfactants is extremely difficult. The addition of mixed bovine SP-B/SP-C to Exosurf® greatly improves its surface activity and its efficacy in reversing surfactant-deficient pressure-volume mechanics in excised rat lungs [113], documenting that the biochemical components of this surfactant are not adequate substitutes for the hydrophobic apoproteins in activity.

Animal-derived clinical exogenous surfactants themselves also differ substantially in their surface activity and ability to resist inhibitor-induced dysfunction. The consensus of available biophysical and animal research indicates that exogenous surfactants based on extracts of lavaged large aggregate endogenous surfactant in Category I of Table 3 have the greatest overall surface and physiological activity. This reflects the fact that these drugs have close compositional analogy to the mix of phospholipids and hydrophobic proteins in active alveolar surfactant. The surface tension lowering ability of several clinical surfactants during dynamic cycling on a pulsating bubble apparatus (37°C, 20 cycles/min, 50% area compression) is illustrated in Figure 3 from Seeger et al [51]. Suspensions of CLSE (Infasurf®) and Alveofact® were found to reach the lowest minimum surface tensions at the lowest surfactant concentrations among the preparations studied. Category I exogenous surfactants such as CLSE and Alveofact® also resist inhibition by blood proteins more effectively than exogenous surfactants like Survanta® and Curosurf® that are processed from lung tissue [51, 113] (Figure 4).

The biophysical activity differences found between surfactants in general reflect differences in their functional biochemical compositions. For example, the activity differences between CLSE and Survanta® in Figure 3 and Figure 4 relate primarily to differences in the content of SP-B in the two preparations [106, 118, 175]. Survanta has an SP-B content by ELISA of only 0.044% by weight relative to phospholipid, while CLSE (Infasurf®) has an SP-B content of 0.9% by weight that approaches that of lavaged whole surfactant [118]. SP-B is known to be the most active of the hydrophobic surfactant proteins in enhancing the adsorption, dynamic surface activity, and inhibition resistance of phospholipids [118, 176–184]. The addition of bovine SP-B or synthetic SP-B peptides to Survanta® significantly improves its surface and physiological activity towards that of Infasurf and whole surfactant [106, 118, 175] (Figure 5).. Despite its lack of SP-B, other active components such as SP-C in Survanta® allow it to have significant efficacy in some forms of ALI/ARDS as noted earlier (e.g., [130, 131, 133]). Treatment with Survanta® has not been found to give substantial improvements in adult patients with ARDS [137], but Category I exogenous surfactants with the complete mix of surfactant lipids and near-endogenous amounts of both SP-B and SP-C may prove to have increased efficacy.

Activity differences between exogenous surfactants such as shown in Figure 3–Figure 5 are generally larger in magnitude than differences found in clinical comparison trials of surfactant drugs [114–117, 142–145, 168, 169]. This is because basic science studies are able to discriminate phenomena under controlled conditions and with more mechanistic

detail than possible in clinical trials. Patient outcomes in clinical surfactant trials in patients with severe acute respiratory failure (whether they are premature infants or adults) are influenced by multiple variables unrelated to lung surfactant activity. Patient outcomes in surfactant trials can also be affected by secondary phenomena involving drug incorporation into type II cell recycling pathways or combination with small amounts of native surfactant apoproteins in the alveoli [46]. Even placebo-controlled studies of surfactant therapy in premature infants typically required substantial numbers of patients to demonstrate improvements in survival and other long term outcomes (as opposed to acute lung functional improvements) [46]. Mechanism-based differences in activity between exogenous surfactants in correlated biochemical, biophysical, and animal research are thus highly important in assessing and evaluating clinical findings.

VI. Examples of research on new synthetic exogenous surfactants for ALI/ARDS

In addition to investigating the activity and delivery of clinical exogenous surfactants, research is also attempting to develop new synthetic or semi-synthetic surfactants for treating lung injury ([46, 47, 185–188] for review). Synthetic lung surfactants manufactured under controlled conditions in the laboratory have significant potential advantages in purity, reproducibility, and quality control compared to animal-derived preparations. As biological products, animal surfactants have significant batch-to-batch variability that increases the cost and complexity of quality control testing during manufacture. Laboratory-synthesized drugs have the potential to be significantly less expensive over time once the costs of development are recovered, and they can be produced in unlimited amounts. Synthetic surfactants are also free from concerns about animal pathogens such as prions, and they are not subject to cultural or religious issues that can affect the use of bovine- or porcine-derived preparations in some countries. Considerations relating to drug dosage described in the preceding section illustrate the practical importance of synthetic preparations in treating ALI/ARDS, where amounts 50–100 times larger than those used in premature infants are required in adults and older children to achieve an equivalent dose on a body weight basis. A larger total number of surfactant doses per patient may also be necessary in patients with ALI/ARDS, further increasing the total amount of surfactant required. The cost of multiple doses of exogenous surfactant per adult patient would be prohibitive at a level even closely proportional to the expense of current 100–200 mg vials of animal-derived surfactants used in infants. The production of synthetic surfactants could theoretically be scaled up to large amounts with substantially reduced expense so as to allow more cost-effective therapy for ALI/ARDS.

Two important conceptual approaches being followed to develop synthetic exogenous surfactants are: (1) Combining human sequence recombinant proteins or synthetic amphipathic peptides with synthetic biological glycerophospholipids; and (2) combining synthetic amphipathic peptides with novel synthetic lipids designed to have favorable physicochemical properties such as high surface activity and structural resistance to inflammatory phospholipases during lung injury. Surfaxin® (KL4) [87, 107, 123, 189–195] and Venticute® (recombinant SPC surfactant) [26, 196–201] are two current examples of

the first of these approaches (Table 3). However, the 21 amino acid KL4 peptide is only a very rough structural analog to native SP-B, and advances in peptide molecular modeling and synthesis technology support the feasibility of preparing new SP-B peptides with significantly greater sequence and molecular folding specificity, and correspondingly higher activity ([202–204] for review). The development of new synthetic SP-B peptides is particularly important for optimal synthetic exogenous surfactants given the greater activity of SP-B compared to SP-C in native surfactant noted earlier [118, 176–184]. In addition to peptide/protein components in new synthetic surfactants, it is also important to consider their lipid constituents. On a weight or molar basis, lipids are the major components of both endogenous and exogenous lung surfactants. Ester-linked glycerophospholipids of the kind found in native surfactant are the primary lipids used in current synthetic exogenous surfactants. However, synthetic ether-linked lipids are now available that have direct structural analogy to lung surfactant lipids plus designed molecular behavior that enhances adsorption and spreading while maintaining very high dynamic surface tension lowering in surface films (e.g., [71, 205–211]). Moreover, such lipids have structural features making them resistant to phospholipases such as phospholipase A_2, which has been implicated in the pathology of ALI/ARDS [65, 212–218]. Phospholipase-induced degradation of lung surfactant glycerophospholipids not only reduces the concentration of active components, but also generates reaction products such as lysophosphatidylcholine and fluid free fatty acids that can further decrease surface activity by interacting biophysically with remaining surfactant at the alveolar interface [55, 59, 70]. Synthetic exogenous surfactants containing such phosphonolipids combined with purified surfactant proteins or synthetic peptides have very high overall surface activity plus an ability to resist phospholipases in ALI/ARDS [71, 208–211, 219]. On-going basic research is continuing to design and synthesize peptides related to SP-B and other surfactant proteins for use in highly-active fully-synthetic exogenous surfactants in combination with either normal glycerophospholipids or phospholipase-resistant analogs.

VI. Summary and future prospects for surfactant therapy in ALI/ARDS

Exogenous surfactant therapy is now standard in the prevention and treatment of RDS in premature infants, and basic science and clinical evidence support its use in at least some patients with lung injury-associated respiratory failure as described in this article. The efficacy of surfactant therapy in term infants with meconium aspiration is sufficiently documented that this is now a standard intervention in many neonatal intensive care units. Surfactant therapy is also frequently used in neonatal patients with ALI/ARDS (or related acute respiratory failure) from respiratory infections or pneumonia. Controlled trials of surfactant therapy in children with ALI/ARDS have shown significant benefits, with significant survival advantages in direct pulmonary lung injuries as reported in the recent trial of Willson et al [25]. The relative enthusiasm of pediatric intensive care specialists for surfactant therapy in respiratory failure to some extent probably reflects the fact that this intervention was originally defined for neonatal applications. The striking success of surfactant therapy in treating and preventing RDS in premature neonates, and the large body of accompanying basic research on the composition and activity of exogenous surfactants, have thus been particularly apparent to pediatric subspecialists.

Current clinical evidence supporting the use of surfactant in adults with ALI/ARDS is less extensive and compelling than in infants and children. However, the surfactants that have to date been most widely studied in adults with ARDS (Exosurf® and Survanta®) are known to have limitations in composition and activity compared to several other available preparations. Also, adult studies have not focused on direct pulmonary forms of ALI/ARDS, which is where surfactant therapy is most likely to be effective as a targeted intervention. In addition, neonatal data suggest that early surfactant administration generates improved responses compared to delayed administration (e.g., [220]), possibly as a result of better intrapulmonary drug distribution coupled with minimized ventilator-induced lung injury. It would make sense intuitively that similar advantages might accompany early surfactant administration in patients with ALI/ARDS. It is challenging and expensive to examine surfactant therapy in placebo-controlled clinical trials of substantial size in adults with ALI/ARDS, but further studies of direct pulmonary forms of these conditions treated with the most active available exogenous surfactant preparations are clearly warranted based both on pathophysiological understanding and on extensive biophysical and animal research.

Finally, a major issue with regard to surfactant therapy in ALI/ARDS involves its potential use in combination with agents or interventions that target additional aspects of the complex pathophysiology of acute pulmonary injury. This kind of combination therapy approach may be particularly important in adults with ALI/ARDS, where responses to exogenous surfactant have so far been disappointing. The use of multiple therapeutic agents or interventions based on specific rationales for potential synergy has the potential to significantly enhance patient outcomes in complex disease processes involving inflammatory lung injury. The potential use of exogenous surfactant therapy in the context of specific combined-modality interventions is described in detail elsewhere [119, 221, 222]. Examples of agents that might be synergistic with exogenous surfactant in ALI/ARDS include anti-inflammatory drugs such as steroids or receptor antagonists, antioxidants, and vasoactive drugs such as inhaled nitric oxide (iNO). In addition, specific ventilator modalities or ventilation strategies that reduce iatrogenic lung injury may be equally important to consider in conjunction with surfactant therapy. Given the known importance of surfactant dysfunction in inflammatory lung injury, it is likely that surfactant therapy alone or in combination with other agents will be applicable for adult as well as pediatric patients with ALI/ARDS associated with direct pulmonary injury.

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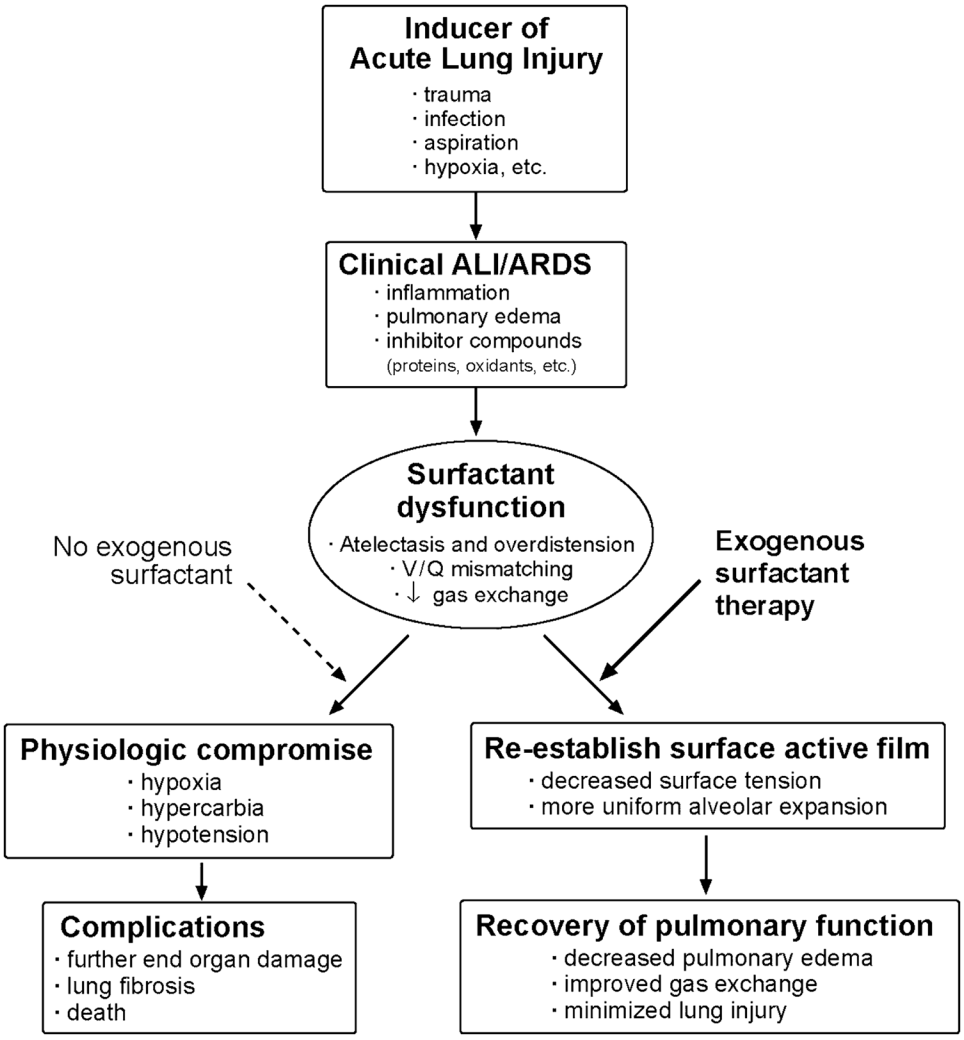

Figure 1. Schematic of the rationale for exogenous surfactant therapy to mitigate surfactant dysfunction in ALI/ARDS

The pathophysiology of acute inflammatory lung injury includes surfactant dysfunction, which contributes to respiratory failure in term infants, children, and adults with clinical acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Surfactant dysfunction reduces lung volumes and compliance, causes atelectasis and overdistension, increases ventilation/perfusion (V/Q) mismatching, and reduces gas exchange. In addition, surfactant dysfunction and lung injury can also be present in the clinical course of premature infants being treated with mechanical ventilation and supplemental oxygen for surfactant deficient lung disease in association with the neonatal respiratory distress syndrome (RDS). Scientific understanding indicates that surfactant dysfunction in lung injury can, at least in principle, be ameliorated by exogenous surfactant therapy as discussed in this article.

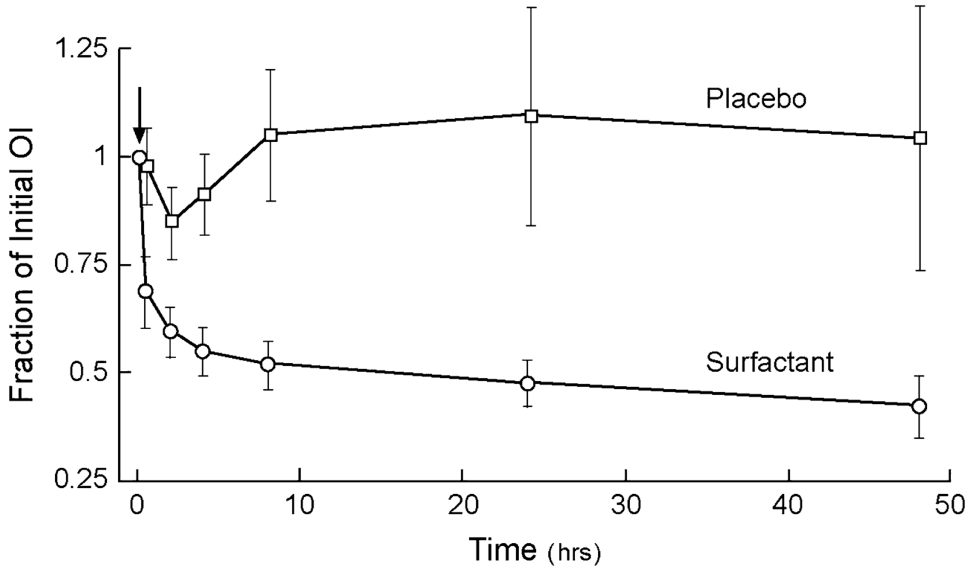

Figure 2. Improvements in oxygenation index (OI) after instillation of exogenous surfactant in children with ALI/ARDS

Patients ranging in age from 1 day through 18 years in eight pediatric intensive care units were randomized to surfactant or control groups. Surfactant-treated patients received a dose of Infasurf® of 80 mL/m^2 body surface (70 mg/kg body weight) by tracheal instillation during hand-ventilation with 100% oxygen (arrow). Control patients received hand-ventilation and 100% oxygen alone. Ten of 21 surfactant-treated patients received a second dose 12 or more hours after the first. Significant improvements were found in lung function in patients receiving exogenous surfactant therapy. OI is defined as: 100 × MAP × FiO_2/PaO_2, where MAP = mean airway pressure; FiO_2 = fraction of inspired oxygen; PaO_2 = arterial partial pressure of oxygen. Data from Willson et al [125].

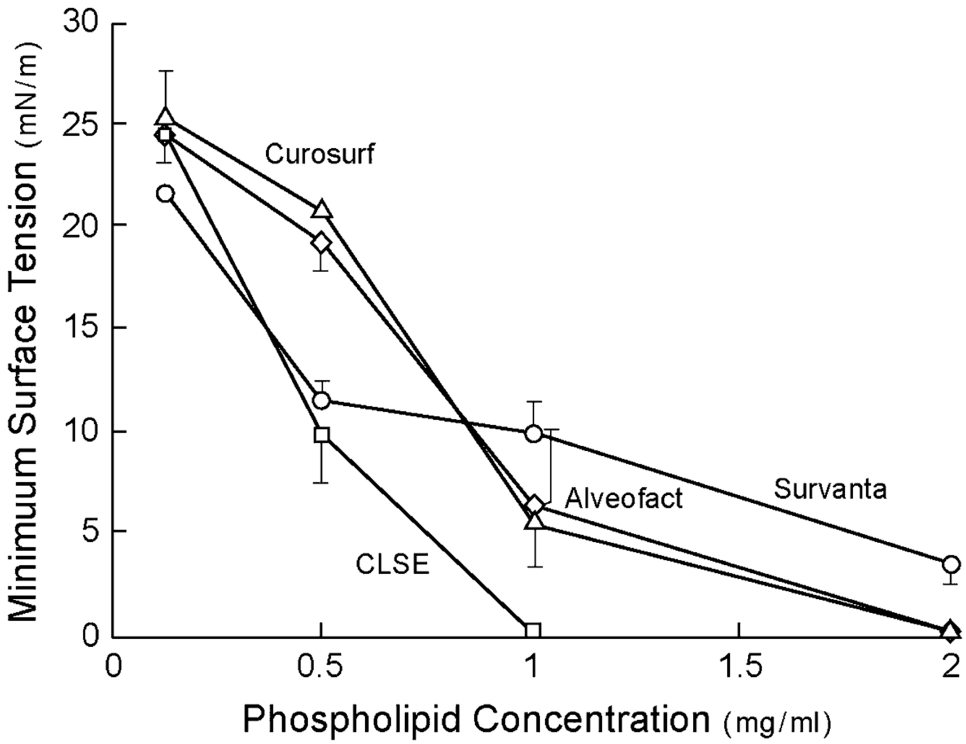

Figure 3. Overall surface tension lowering ability of clinical exogenous surfactants

Minimum surface tension after 5 minutes of pulsation in a bubble surfactometer (37°C, 20 cycles/min, 50% area compression) is plotted as a function of surfactant phospholipid concentration for several clinical surfactants. The surfactants shown vary widely in overall surface tension lowering ability, with the most active being Category I surfactants from Table 3 (e.g., Infasurf® and Alveofact®). Data redrawn from Seeger et al [51].

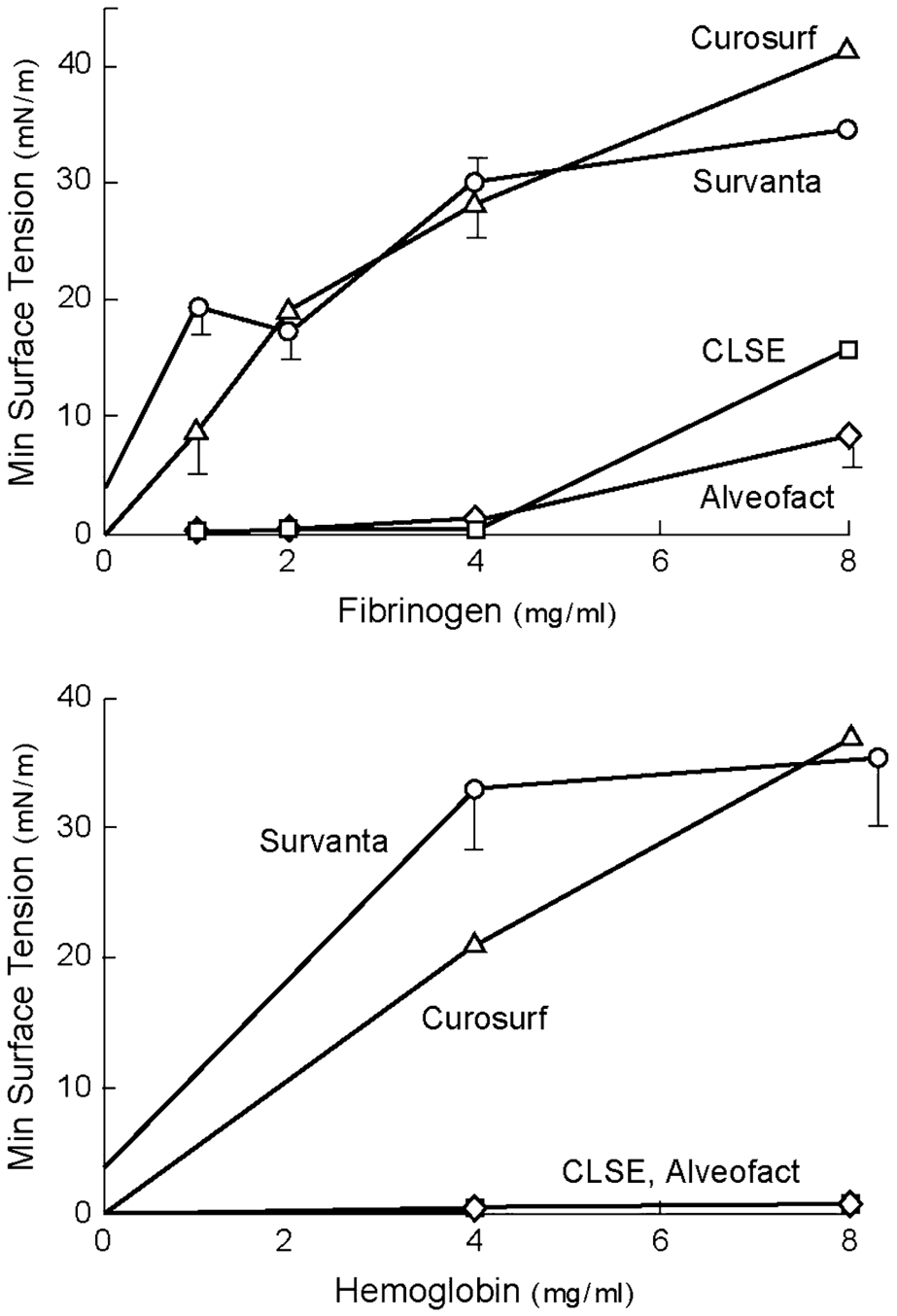

Figure 4. Resistance of clinical surfactants to inhibition by blood proteins

Minimum surface tension after 5 minutes of pulsation in a bubble surfactometer (37°C, 20 cycles/min, and 50% area compression) is plotted against the concentration of inhibitory blood proteins (fibrinogen and hemoglobin). The results indicate that animal-derived exogenous surfactants that closely mimic natural surfactant by being extracted from lung lavage (Category I surfactants from Table 3) have an improved ability to resist inhibition by plasma proteins compared to the other preparations shown. Surfactant phospholipid concentration was 2 mg/ml. Redrawn from [51].

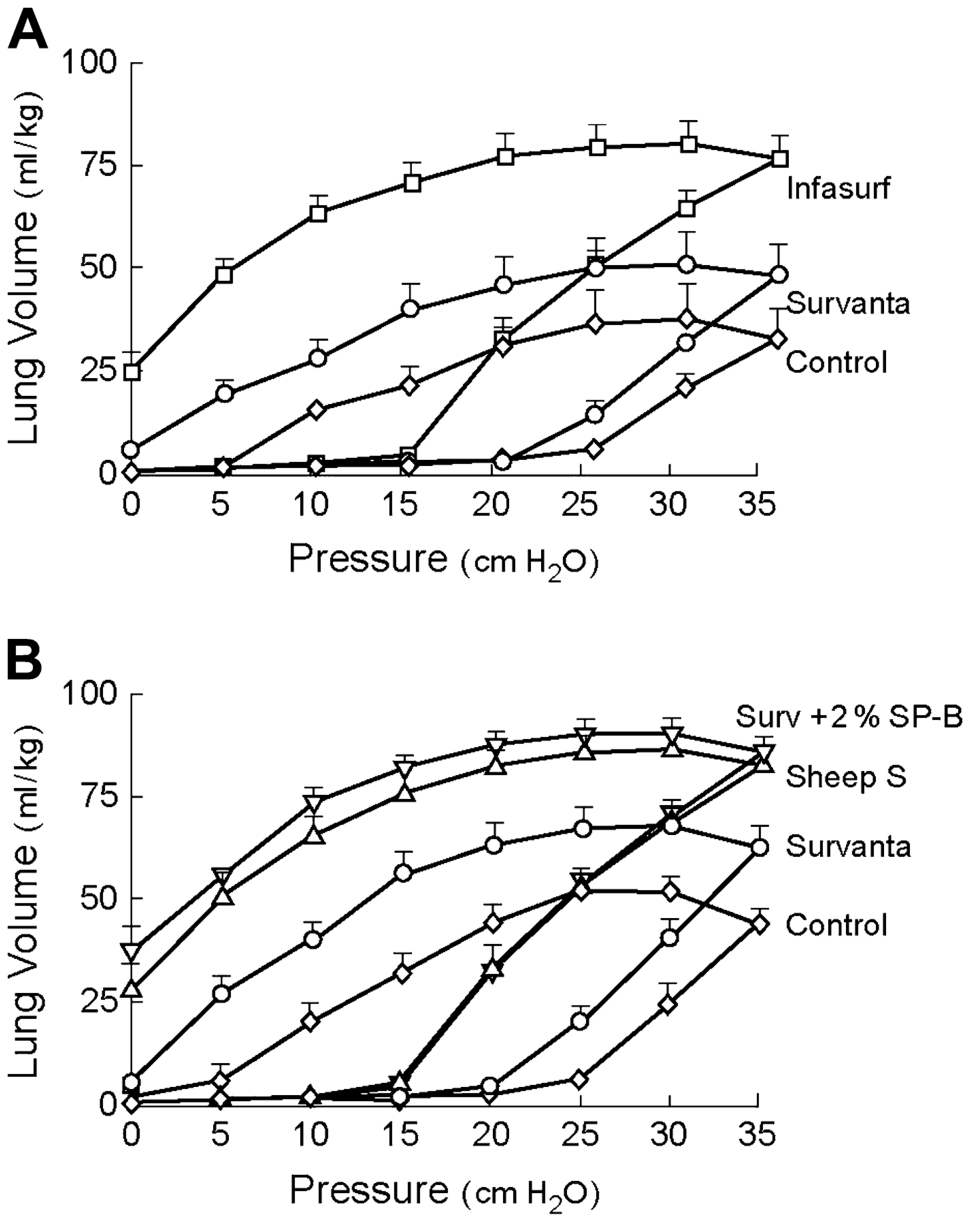

Figure 5. Effects on physiological activity from the addition of purified SP-B to Survanta®

(Top): Premature rabbit fetuses (27 days gestation) treated with Survanta® or Infasurf®, and untreated controls; (Bottom): Premature rabbit fetuses treated with Survanta®, Survanta® + SP-B (2% by wt by ELISA), natural surfactant from adult sheep (Sheep S), or untreated controls. Infasurf® improved lung mechanics more than Survanta® (top panel), and the importance of SP-B in this behavior is shown by the increased activity of Survanta® + SP-B compared to Survanta® alone (bottom panel). Surfactants were instilled intratracheally at a dose of 100 mg/kg body weight, and quasistatic P-V curves were measured following 15 min of mechanical ventilation. Data are redrawn from Mizuno et al [175].

Table 1

Mortality rates reported in a series of studies in pediatric ALI/ARDS.

Author	Year	# Patients	Mortality (%)
Pfenninger [15]	1982	20	40%
DeBruin [21]*	1992	100	72%
Timmons [22]	1995	470	43%
Dahlem [23]	2003	44	27.3%
Curley [24]	2005	102	8%
Willson [25]	2005	152	28%
Flori [19]	2005	328	22%
Pediatric Study Group (ANZICS) [20]	2007	117	35%

* Patients consisted of mostly immune compromised children

Table 2

Animal models of ALI/ARDS lung injury that have been shown to respond acutely to exogenous surfactant therapy.

Aspiration of acid [82–84]or meconium [85–88]
Anti-lung serum infusion [89]
Bacterial or endotoxin-induced injury [90–95]
Bilateral vagotomy [96]
Hyperoxic lung injury [97–101]
In vivo lung lavage with mechanical ventilation [102–107]
NNNMU-induced lung injury [108–110]
Viral pneumonia [111, 112]

NNNMU is N-nitroso-N-methylurethane. See text for discussion.

Table 3

Clinical exogenous surfactant drugs for treating diseases that involve lung surfactant deficiency or dysfunction.

I.	**Organic solvent extracts of lavaged animal lung surfactant**
	Infasurf® (CLSE)
	bLES®
	Alveofact®
II.	**Supplemented or unsupplemented organic solvent extracts of processed animal lung tissue**
	Survanta®
	Surfactant-TA®
	Curosurf®
III.	**Synthetic exogenous lung surfactants**
	Exosurf®
	ALEC®
	Surfaxin® (KL4)
	Venticute® (Recombinant SP-C surfactant)

Curosurf ® (Chesi Farmaceutici and Dey Laboratories), Infasurf® (ONY, Inc and Forest Laboratories), and Survanta® (Abbott/Ross Laboratories) are currently FDA-approved in the USA, and Surfaxin® (KL4, Discovery Laboratories) is under clinical evaluation. Exosurf® (Glaxo-Wellcome) is also FDA-approved, but is no longer used clinically. Details on the composition, activity, and efficacy of these surfactants in treating or preventing RDS in premature infants are detailed elsewhere (e.g., [46]), and this article focuses on their use in ALI/ARDS. See text for details. Table adapted from Refs [46, 119].

Table 4

Clinical studies reporting benefits of exogenous surfactant therapy in acute respiratory failure (ALI/ARDS).

Study	Patients (N)	Disease Or Syndrome	Surfactant	Outcomes
Güntheret al [120]	Adults (27)	ARDS	Alveofact®	Improved surfactant function
Walmrath et al. [155]	Adults (10)	ARDS from sepsis	Alveofact®	Improved oxygenation
Spragg et al [122]	Adults (6)	ARDS from multiple causes	Curosurf®	Improved oxygenation a and biophysical function
Wiswell et al [123]	Adults (12)	ARDS from multiple causes	Surfaxin®	Improved oxygenation
Willson et al [124, 125]	Children (29 & 42)	ARDS from multiple causes	Infasurf®	Improved oxygenation
Willson et al [25]	Children(152)	ARDS from multiple causes	Infasurf®	Improved survival, and improved ventilation
Lopez-Herce et al [126]	Children (20)	ARDS + post-op cardiac	Curosurf®	Improved oxygenation
Hermon et al [127]	Children (19)	ARDS + post-op cardiac	Curosurf® or Alveofact®	Improved oxygenation
Herting et al [128]	Children (8)	Pneumonia	Curosurf®	Improved oxygenation
Auten et al [129]	Infants (14)	Meconium aspiration or pneumonia	Infasurf®(CLSE)	Improved oxygenation
Lotze et al [130, 131]	Infants (28 & 328)	ECMO, multiple indications	Survanta®	Improved oxygenation, decreased ECMO
Khammash et al [132]	Infants (20)	Meconium aspiration	bLES®	Improved oxygenation in 75% of patients
Findlay et al [133]	Infants (40)	Meconium aspiration	Survanta®	Improved oxygenation, decreased pneumothorax and mechanical ventilation
Luchetti et al [134, 135]	Infants (20 & 40)	RSV bronchiolitis	Curosurf®	Improved oxygenation

Tabulated clinical studies include both controlled and non-controlled trials as discussed in the text.

Table 5

Clinical outcomes from a recent controlled study using exogenous surfactant (Infasurf®; calfactant) in pediatric patients with ALI/ARDS [25].

	Calfactant (n=77)	Placebo (n=75)	P Value
Mortality			
Died (in hospital)	15 (19%)	27 (36%)	0.03
Died w/o extubation	12 (16%)	24 (32%)	0.02
Failed CMV*	13 (21%)	26 (42%)	0.02
ECMO	3	3	--
Use of Nitric Oxide	9	10	0.80
HFOV after entry	7	15	0.07
Secondary Outcomes			
PICU LOS	15.2 ± 13.3	13.6 ± 11.6	0.85
Hospital LOS	26.8 ± 26	25.3 ± 32.2	0.91
Days O2 therapy	17.3 ± 16	18.5 ± 31	0.93
Hospital Charges#	$205 ± 220	$213 ± 226	0.83
Hospital Charges/day#	$7.5 ± 7.6	$7.9 ± 7.5	0.74

*Some patients that failed CMV had more than one non-conventional therapy (ECMO, iNO, or HFOV);

#Costs are given in thousands of dollars.

Abbreviations CMV = conventional mechanical ventilation; ECMO = extracorporeal membrane oxygenation; HFOV = high frequency oscillatory ventilation; iNO = inhaled nitric oxide. In addition to improving mortality and reducing the percentage of patients that failed CMV as reported in the table, instilled calfactant also significantly improved oxygenation index compared to placebo (P=0.01, data not shown). From Willson et al [25].

Table 6

Efficacy of exogenous surfactant (Infasurf®, calfactant) in direct and indirect forms of lung injury in the controlled study of Willson et al [25] in children up to age 21 with ALI/ARDS.

	Placebo	Calfactant	*P* value
Direct lung injury (n)	48	50	--
OI ↓ 25% or more	31%	66%	0.0006
Ventilator days	17 ± 10	13 ± 9	0.05
Died	38%	8%	0.0005
Indirect lung injury (n)	27	27	--
OI ↓ 25% or more	41%	37%	0.79
Ventilator days	17 ± 10	18 ± 10	0.75
Died	33%	41%	0.65

Percentages of patients with an OI decrease of greater than 25%, days on mechanical ventilation, and percentage mortality were calculated in a post-hoc analysis. The efficacy of exogenous surfactant was confined to patients with direct pulmonary forms of ALI/ARDS. See text for details.