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Surfactant Therapy of ALI and ARDS

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Abstract

This article examines exogenous lung surfactant replacement therapy and its utility in mitigating clinical acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Biophysical research has documented that lung surfactant dysfunction can be reversed or mitigated by increasing surfactant concentration, and multiple studies in animals with ALI/ARDS have shown that respiratory function and pulmonary mechanics *in vivo* can be improved by exogenous surfactant administration. Exogenous surfactant therapy is a routine intervention in neonatal intensive care, and is life-saving in preventing or treating the neonatal respiratory distress syndrome (NRDS) in premature infants. In applications relevant for lung injury-related respiratory failure and ALI/ARDS, surfactant therapy has been shown to be beneficial in term infants with pneumonia and meconium aspiration lung injury, and in children up to age 21 with direct pulmonary forms of ALI/ARDS. However, extension of exogenous surfactant therapy to adults with respiratory failure and clinical ALI/ARDS remains a challenge. Coverage here reviews clinical studies of surfactant therapy in pediatric and adult patients with ALI/ARDS, particularly focusing on its potential advantages in patients with direct pulmonary forms of these syndromes. Also discussed is the rationale for mechanism-based therapies utilizing exogenous surfactant in combination with agents targeting other aspects of the multifaceted pathophysiology of inflammatory lung injury. Additional factors affecting the efficacy of exogenous surfactant therapy in ALI/ARDS are also described, including the difficulty of effectively delivering surfactants to injured lungs and the existence of activity differences between clinical surfactant drugs.

I. Introduction

The extensive pulmonary alveolar and capillary networks make the lungs highly susceptible to cell and tissue injury from pathogens or toxic environmental agents present either in the circulation or in the external environment. The medical consequences of acute pulmonary injury are frequently defined as the syndromes of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The American-European Consensus Conference (AECC) in 1994 defined ARDS as respiratory failure of acute onset with a PaO_2/FiO_2 ratio ≤200 mmHg (regardless of the level of positive end expiratory pressure, PEEP), bilateral infiltrates on frontal chest radiograph, and a pulmonary capillary wedge pressure <18 mmHg (if measured) or no evidence of left atrial hypertension [1]. ALI is defined identically except

for a higher PaO_2/FiO_2 limit of <300 mmHg [1]. The AECC definitions of ALI/ARDS are widely-used clinically, although they have nontrivial deficiencies in discrimination. The AECC definitions are often 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. Expanded definitions of ALI/ARDS have also been developed using the Delphi technique [8].

The incidence of ALI/ARDS has been variably reported to be 50,000–190,000 cases per year in the United States [1, 9–15]. Comprehensive studies by Rubenfeld et al [14] and Goss et al [15] have placed the incidence of ALI at 22–86 cases per 100,000 persons per year [14, 15], with 40–43 percent of these patients having ARDS [14]. The incidence of ALI/ARDS is lower in pediatric age groups, but still equates to thousands of affected children per year [16–20]. Overall mortality rates in adult and pediatric patients with these lung injury syndromes still remain very high at 25–50% [1, 9–15, 17–20]. Rubenfeld et al [14] 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. Further details on the incidence and mortality of ALI/ARDS are given elsewhere in this issue of *Critical Care Clinics*.

There is clearly a significant need for improved therapy of ALI/ARDS, and this article focuses primarily on the potential benefits of exogenous surfactant replacement. In targeting this and other therapeutic interventions to the most applicable subgroups of patients, it is helpful to distinguish between ALI/ARDS associated with direct pulmonary causes compared to systemic (indirect, extra-pulmonary) causes (Table 1). Direct pulmonary causes of ALI/ARDS include pulmonary viral or bacterial infections, aspiration (e.g., gastric aspiration, meconium aspiration in infants), blunt thoracic trauma with lung contusion, near-drowning, thoracic radiation, and the inhalation of oxygen, smoke or other toxicants. Indirect (systemic) causes of ALI/ARDS include sepsis, closed space burn injury, hypovolemic shock, generalized trauma with long bone fracture, multiple transfusions, pancreatitis, and other primary extra-pulmonary insults. Indirect forms of ALI/ARDS have substantial multi-organ pathology that significantly affects long term patient outcomes, reducing the impact and effectiveness of pulmonary-based therapies like exogenous surfactant administration. As detailed later, post-hoc analyses in two clinical trials of surfactant therapy in ALI/ARDS suggest greater efficacy in direct as opposed to indirect forms of pulmonary injury [21, 22].

II. Surfactant dysfunction in ALI/ARDS

There are a number of pathways by which lung surfactant activity can be compromised during acute pulmonary injury, as summarized schematically in Figures 1 and 2. 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 [23–35]. Research over the last two decades has clarified many pathways and mechanisms contributing to surfactant dysfunction in acute pulmonary injury (for detailed review see [36–38]). One important mechanism of surfactant dysfunction in ALI/ARDS involves detrimental physicochemical interactions with substances in the alveoli as a result of permeability edema or inflammation (Table 2). Extensive biophysical studies has documented that the surface activity of lung surfactant is significantly impaired by injury-related inhibitors such as plasma and blood proteins [39–46], meconium [47], cell membrane lipids [41, 46, 48], fluid free fatty acids [46, 49–51], reactive oxidants [49, 52–54], and lytic enzymes including proteases [55] and phospholipases [56, 57]. Mechanistically, albumin and other blood proteins impair surface activity primarily by competitive adsorption that reduces the entry of

active surfactant components into the alveolar air-water interface [43, 58]. In contrast, cell membrane lipids, lysophospholipids, or fatty acids act in part by mixing into the surface film and compromising its ability to reach low surface tension during dynamic compression [41, 46, 50, 58]. Phospholipases, proteases, and reactive oxygen-nitrogen species act to chemically alter functionally-essential surfactant lipids or proteins [55, 57, 59]. Importantly, it is well-documented that surface activity deficits from all these mechanisms can be mitigated *in vitro* by increasing the concentration of active surfactant even if inhibitor substances remain present [36–38], supporting the conceptual utility of exogenous surfactant supplementation strategies.

Another type of surfactant dysfunction that occurs in many forms of lung injury is the depletion or alteration of active large surfactant 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 [51, 60–66]. Total lavaged surfactant phospholipid is unchanged or even increased in amount in many animal models of ALI/ARDS, but the percentage of large surfactant aggregates is frequently reduced and the activity of remaining aggregates impaired [51, 67–70]. The percentage of large aggregates and their content of SP-A and SP-B have also been shown to be reduced in bronchoalveolar lavage from patients with ARDS [28–30]. Large surfactant aggregates can in principle be affected by several pathways in ALI/ARDS, including physical interactions with injury-induced substances in the alveoli, alterations in intra-alveolar aggregate processing, or changes in surfactant reuptake, metabolism or recycling in type II cells [51, 67–70]. Again, depleted large aggregates can theoretically be replenished by delivering supplemental exogenous surfactant.

Surfactant dysfunction including both inhibitor-induced activity reductions and large aggregate depletion has been widely-demonstrated in animal models of acute inflammatory lung injury *in vivo* [36, 37, 70–79]. The ability of exogenous surfactant therapy to improve acute respiratory pathology in animal models of ALI/ARDS *in vivo* is similarly well-documented (Table 3). Examples of animal models found to display acute improvements in arterial oxygenation and/or lung mechanics following surfactant therapy are: acid aspiration [80–82], meconium aspiration [83–86], anti-lung serum [87], bacterial or endotoxin injury [88–93], pulmonary contusion[78], bilateral vagotomy [94], hyperoxia [95–99], *in vivo* lavage [100–105], N-nitroso-N-methylurethane (NNNMU) injury [106–108], and viral pneumonia [109, 110]. Animals studies of acute injury are typically not designed to assess efficacy based on long-term outcomes. However, improvements in acute respiratory function should ultimately be associated with improved long-term outcomes if they are not outweighed by other untreated and continuing aspects of lung injury pathology in patients with ALI/ARDS.

III. Factors affecting the efficacy of exogenous surfactant therapy in ALI/ARDS

A number of factors make developing exogenous surfactant therapy for ALI/ARDS more difficult compared to the case of surfactant-deficient premature infants with the neonatal respiratory distress syndrome (NRDS). Premature infants with NRDS have a primary deficiency of surfactant due to a lack of mature alveolar type II epithelial cells at birth. The delivery of exogenous surfactant at or near parturition thus provides a direct and specific treatment for the disease, normalizing respiration until sufficient numbers of functional type II cells are available to synthesize/secrete active endogenous surfactant. Type II cell maturation commonly occurs over a matter of days even in quite premature infants if the lungs are not significantly injured by mechanical ventilation and oxygen therapy during intensive care. Exogenous surfactant is also typically given to premature infants in the immediate post-natal period when pulmonary edema and inflammation are minimal, and

drug delivery and distribution following intra-tracheal instillation is facilitated further by the absorption of fetal lung liquid that occurs at this time. This combination of specificity in terms of therapeutic target (surfactant deficiency) plus drug deliverability makes surfactant therapy in NRDS effective and life-saving in premature infants.

In ALI/ARDS, the major rationale for surfactant therapy is the presence of surfactant dysfunction in the injured lungs, although the therapy also will treat surfactant deficiency if present. Surfactant dysfunction in ALI/ARDS is most prominent in the acute exudative phase of disease, and it is here where surfactant therapy has the greatest theoretical benefits. However, several complexities not present in the case of NRDS exist. While all forms of ALI/ARDS share aspects of lung injury, these conditions are clinical syndromes encompassing diverse etiologies with individual features and varying levels of lung injury and systemic pathology. Combining this pathophysiological heterogeneity under the single rubric of ALI/ARDS significantly reduces the resolving power of clinical trials. The use of sub-classifications such as “direct pulmonary” and “indirect systemic” forms of ALI/ARDS as in Table 1 helps to address some of this heterogeneity, but broad groups of individuals with multiple etiologies are still combined. Moreover, even for patients with a single lung injury cause, the pathology present is much more complicated than simple surfactant deficiency of prematurity. Acute pulmonary injury has a complex and multifaceted pathology that includes not only surfactant dysfunction, but also prominent aspects of inflammation, vascular dysfunction, oxidant injury, cellular injury, and edema. Edema and inflammation in patients with ALI/ARDS make it more difficult to deliver and distribute exogenous surfactant to the alveoli. Also, the presence of significant aspects of pathology not targeted by surfactant therapy may substantially affect patient outcomes, making it more difficult to discern the intrinsic efficacy of this intervention *per se*. The complex pathophysiology of acute pulmonary injury is a major factor in the rationale for combination therapy approaches in ALI/ARDS as described in a later section. However, whether one deals with single agent or combination interventions, evaluating clinical therapies in ALI/ARDS in terms of outcomes such as survival requires multi-center controlled studies of substantial size, with patient populations and outcome variables chosen as rigorously as possible [111].

IV. Clinical exogenous surfactant drugs

In order to be effective in ALI/ARDS, exogenous surfactants must have high intrinsic surface activity plus the ability to resist inactivation. Clinical exogenous surfactants used to treat surfactant-related lung disease are listed in Table 4. The table classifies clinical surfactants into three groups: (I) organic solvent extracts of lavaged endogenous lung surfactant from animals; (II) organic solvent extracts of processed animal lung tissue with or without additional synthetic additives; and (III) synthetic preparations not containing animal-derived material. Meaningful evaluations of surfactant therapy in ALI/ARDS must account for differences in surfactant drug activity and inhibition resistance that can significantly impact therapeutic efficacy, and many such differences stem from composition-based differences as noted below.

Organic solvent extracts of lavaged alveolar surfactant (Category I in Table 4) in principle contain all the lipids and hydrophobic proteins in endogenous surfactant, although composition can still vary in among preparations because of differences in extraction and processing methods. Surfactant preparations extracted from minced or homogenized lungs (Category II) contain some non-surfactant tissue-derived components, and also require more elaborate processing that can alter composition relative to native surfactant. For example, the content of functionally-important surfactant protein SP-B is reduced to a very low level in Survanta® during processing from bovine lungs [42, 112–114]. Synthetic lung surfactants

(Category III) have significant conceptual advantages over animal-derived surfactants in purity, reproducibility, manufacturing quality control efficiency, and scale-up economy. They are also free from the risk of pathogens such as prions, and are not subject to cultural/religious considerations affecting bovine or porcine surfactants. However, it has proved to be challenging to bioengineer fully-synthetic surfactants having high activity equivalent to native surfactant.

Two early synthetic surfactants (Exosurf® and ALEC) are no longer used clinically because of their lower activities relative to animal-derived surfactants. The synthetic preparation KL4 (Surfaxin®) contains a 21 amino acid peptide that roughly approximates the ratio of positive and uncharged amino acid residues in SP-B [115, 116], but does not incorporate active regions of molecular structure of the human protein, while recombinant SP-C surfactant (Venticute®) contains no SP-B peptide. Recent advances in molecular bioengineering and peptide chemistry have increased the potential to design and produce new highly-active synthetic lung surfactants, and several approaches are currently being studied (see [117–120] for review). This includes fully-synthetic lipid/peptide surfactants bioengineered to contain peptides incorporating the most active amino acid sequences in human SP-B, such as Super Mini-B peptide [121]. Synthetic exogenous surfactants containing Super Mini-B or related peptides that mimic active human SP-B can also incorporate novel lipids with beneficial molecular properties such as phospholipid-resistance. One particularly active synthetic lipid analog of dipalmitoyl phosphatidylcholine (DPPC), the most prevalent phospholipid in native surfactant, is the phospholipase-resistant diether compound designated DEPN-8 [117, 122–125]. Synthetic surfactants containing DEPN-8 or other phospholipase-resistant lipids plus active SP-B peptides may have particular potential utility in treating ALI/ARDS [59, 117, 124–127], where these lytic enzymes can be elaborated in high concentrations in the interstitium and alveoli of injured lungs [128–134]. New synthetic surfactants can also potentially be bioengineered to include novel peptide components incorporating the most active regions of other human surfactant apoproteins in combination with SP-B peptides and lipids [117].

V. Clinical experience with exogenous surfactant therapy in ALI/ARDS

A number of clinical studies have reported pulmonary benefits following the instillation of exogenous surfactants to term infants, children, or adults with lung injury-related acute respiratory failure or ALI/ARDS [21, 135–150] (Table 5). However, many of these positive clinical studies are small case studies or treatment trials that documented improvements only in acute lung function (oxygenation). Randomized controlled trials of surfactant therapy in patients with ALI/ARDS have had limited success in improving long-term outcomes including survival, particularly in adults [151, 152]. Nonetheless, there are several populations of patients with lung injury-related respiratory failure where therapy with active exogenous surfactant drugs has been documented to be effective in improving clinically-significant outcomes. This is particularly true in pediatric patients, encompassing full-term infants through older children including young adults up to age 21. No studies on surfactant use in infants, children, or adults have shown any significant adverse long-term effects from the therapy, although transient hypoxia and some hemodynamic instability surrounding intratracheal or bronchoscopic instillation are common. More detailed review of specific studies of surfactant therapy in various age groups with lung injury is given below.

Surfactant therapy in preterm infants with established Neonatal respiratory distress syndrome NRDS

Multiple studies confirm the efficacy of surfactant therapy in preventing and treating NRDS in preterm infants (e.g., see the meta-analyses in Refs. [153, 154]). It has been established that the use of surfactant for treatment of NRDS is associated with a decreased risk of

pneumothorax, pulmonary interstitial emphysema, bronchopulmonary dysplasia and a decreased risk of mortality [153](Figure 3). Furthermore, multiple doses resulted in greater improvements in oxygenation and ventilator requirements, a decreased risk of pneumothorax, and a trend toward improved survival [154].

Surfactant therapy in term infants with acute respiratory failure

The best-studied use of surfactant therapy in term infants with acute pulmonary injury is in meconium aspiration syndrome [144–148]. When aspirated during delivery, usually in association with fetal distress, meconium obstructs the airways and causes severe inflammatory lung injury. Meconium also acts biophysically to directly inhibit lung surfactant activity [47, 155]. Initial uncontrolled studies by Auten et al [144] and Khammash et al [147] reported significant improvements in lung function following exogenous surfactant administration to term infants with meconium aspiration. Subsequently, Findlay et al [148] studied 40 term infants randomized to surfactant-treated and placebo groups, and showed that this therapy not only improved oxygenation, but also led to a reduced incidence of pneumothorax, a decreased duration of mechanical ventilation and oxygen therapy, a reduced time of hospitalization, and fewer infants meeting criteria for ECMO. Beneficial results from exogenous surfactant administration have also been found in two controlled studies by Lotze et al [145, 146] in term infants referred for ECMO with severe acute respiratory failure (meconium aspiration was a prevalent diagnosis in these patients). In an initial study, 28 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 [145]. A larger multicenter controlled trial in 328 term infants also reported significant improvements in respiratory status and a reduction in the need for ECMO following surfactant treatment [146].

In addition to having efficacy in treating meconium aspiration, surfactant therapy also has clinical benefits in term infants with acute respiratory failure from respiratory syncytial virus (RSV) infection [149, 150, 156]. Luchetti et al [149] reported that 10 infants with severe RSV-bronchiolitis treated with tracheally-instilled porcine-derived surfactant (Curosurf®, 50 mg/kg body weight) had improved gas exchange, a reduced duration of mechanical ventilation, and a reduced length of stay in the pediatric intensive care unit compared to an equal number of control infants not receiving exogenous surfactant. A subsequent multicenter controlled trial in 40 infants with RSV-associated respiratory failure showed that instillation of Curosurf® improved gas exchange and respiratory mechanics, and shortened the duration of mechanical ventilation and hospitalization [150]. Tibby et al [156] also 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 administration is now used in many neonatal intensive care units as a standard treatment for 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 [157, 158].

Surfactant therapy in children with ALI/ARDS

Exogenous surfactant therapy has also been found to be beneficial in improving lung function in children with ARDS-related respiratory failure [21, 139, 140]. In an initial treatment study in 29 children (0.1 to 16 years of age) with acute respiratory failure at 6 centers, Willson et al [139] showed that instillation of Infasurf® (70 mg/kg) improved lung function defined prospectively as a 25% decrease in Oxygenation Index (OI = 100 × Mean Airway Pressure × FiO_2/PaO_2). A subsequent randomized controlled trial in 42 children (ages 1 day to 18 years) at eight centers demonstrated that patients receiving one or two doses of

Infasurf® (70 mg/kg instilled intratracheally in four aliquots) had significantly better OI values over the 50 hours post-treatment [140] (Figure 4. Statistically-significant differences in survival were not found in this relatively small study, but several prospectively-chosen outcome variables including days of mechanical ventilation and days in the intensive care unit were significantly improved by Infasurf®. Surfactant-treated patients also had a significant increase in "ventilator free days" during the first 14 days of hospitalization and a higher incidence of extubation by 72 hours [140]. Moller et al [159] also 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 [21] 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 6). Patients aged 1 wk through 21 years in this twenty-one 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 6). 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 7).

Surfactant therapy in adults with ALI/ARDS

In adults with ALI/ARDS, uncontrolled treatment studies have documented improved respiratory function (oxygenation) with surfactant administration [135, 136], but results from controlled clinical trials have been less successful. An initial large and highly-visible prospective controlled study of surfactant therapy in adults with ARDS in 1996 was definitively negative [151]. Anzueto et al [151] 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 sepsis is an indirect cause of ALI/ARDS that has substantial systemic pathology. Moreover, detailed laboratory and clinical studies have documented that Exosurf® has low activity compared to animal-derived surfactants [42, 160–168], and the drug is no longer used in the United States for this reason. Additionally, the aerosol method of surfactant administration employed by Anzueto et al [151] has not been shown to be as effective as direct airway instillation in delivering and distributing surfactant to the alveoli. A second disappointing controlled clinical trial of surfactant therapy in adults with ALI/ARDS was that of Gregory et al [152] in 1997, who reported small benefits in oxygenation in the subgroup of 43 patients who received four 100 mg/kg doses of Survanta®, but no advantage in survival. However, this trial again focused on sepsis-induced lung injury where significant systemic pathology is present. In addition, Survanta® contains only very small amounts of surfactant protein (SP)-B [42, 112–114], which is the most biophysically active apoprotein in native surfactant [169–177].

In 2003, Spragg et al [22] carried out a controlled trial of recombinant SP-C surfactant (Venticute®) in adults with ARDS and reported immediate improvements in oxygenation, but no 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 [22]. A recent large follow up trial randomized adults with ARDS in association with direct lung injury from pneumonia or aspiration to receive Venticute® (up to 8 doses administered over 96 hours, n=419) or usual care

(n=424)[178]. However, there was no improvement in oxygenation from Venticute® in this large study [178]. In examining this lack of efficacy, the study authors reported that a partial inactivation of rSP-C surfactant occurred in the clinical trial due to a step in the re-suspension process (shear-induced loss of drug activity) [178]. Also, as noted in an earlier section, Venticute® contains rSP-C but not highly active SP-B. There is thus a continuing need for further evaluations of surfactant therapy in adults with ARDS using the most active and inhibition-resistant drugs. In addition, effective delivery of exogenous surfactants to the alveoli must also be accomplished in trials of surfactant therapy in ARDS, as discussed below.

VI. Delivery and dosage of exogenous surfactants in ALI/ARDS

Delivery of exogenous surfactant

In order to effectively treat surfactant dysfunction in injured lungs, exogenous surfactants of high activity must be delivered in adequate concentrations to the alveoli (the actual site of surfactant action). The primary method used to administer exogenous surfactants to patients in ALI/ARDS is intratracheal instillation through an endotracheal tube, as is done in the case of premature infants. Airway instillation of surfactant via a bronchoscope is also sometimes employed in older patients as an alternative. Exogenous surfactant material instilled into the larger airways has the capacity to spread and distribute to the periphery of the lung [179–181]. Spreading from central airways towards the alveoli is promoted by surface tension gradients, i.e., surface tension is reduced in the initial region where surfactant is instilled, and transport is then driven toward peripheral regions where surface tension is higher and surfactant concentration is lower.

The delivery and distribution of instilled exogenous surfactants in injured lungs can potentially be facilitated by the use of specific modes or strategies of mechanical ventilation. For example, studies have suggested that the distribution and/or efficacy of instilled exogenous surfactant can be improved by jet ventilation [182, 183] and partial liquid ventilation [184–186]. 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 [187, 188]. For a given surfactant preparation at fixed shear rate, viscosity can be significantly reduced by modifying the physical formulation by changes in dispersion methodology, ionic environment, or temperature [187, 188].

An alternative to administering exogenous surfactants by instillation is to deliver them in aerosol form. In theory, aerosolization can reduce required surfactant doses if efficient alveolar delivery can be achieved 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 [189–191], and exogenous surfactants have been aerosolized to animals and patients with surfactant deficiency or dysfunction [89, 103, 108, 151, 192–194]. However, the theoretical potential of aerosols to improve alveolar deposition and lower required surfactant doses has not yet been replicated in practice. Aerosol methods to date have not been shown to deliver and distribute exogenous surfactants as effectively as instillation in clinical studies, although this may change in the future as technology for aerosol formation and delivery advances. A recent report, using dry powder aerosolization of surfactant protein C in animal models of acute lung injury, showed that a large amount of delivery of the surfactant with intact biophysical properties was achievable[195].

Dosage of exogenous surfactants

Typical doses of surfactant drugs instilled intratracheally in premature infants with NRDS are 100mg/kg body weight. This represents a significant excess over the amount needed to cover the surface of the alveolar network with a tightly-packed surfactant film (only about 3 mg/kg of phospholipid-rich surfactant at an average 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 [37, 190]). Excess exogenous surfactant that reaches the alveoli following instillation provides a reservoir of material in the hypophase that can adsorb into the air-water interface when needed, and excess surfactant is also available for incorporation into endogenous surfactant pools via type II cell uptake and recycling pathways.

For ALI/ARDS, surfactant dosage amounts are typically scaled up on a body weight (or body surface area) basis. For older children and adults, this represents a substantial increase in the total amount of surfactant that needs to be administered. To achieve a comparable dose to the 100 mg/kg level used in premature infants weighing one kilogram, the prototypical “70 kg adult” requires 7 grams of exogenous surfactant. Clinical studies instilling exogenous surfactants in patients with ALI/ARDS have used a range of doses as high as 300 mg/kg [196] and as low as 25 mg/kg [22]. An instilled dose of 100 mg/kg in an adult with ALI/ARDS requires an instilled fluid volume of about 90–280 ml at the phospholipid concentrations of current clinical surfactant drugs in saline (~25–80 mg/ml). Although it is clearly important to minimize instilled surfactant volumes in patients with edema and severe respiratory failure, this is something of a two-edged sword. In particular, instilled surfactant volume can impact intrapulmonary distribution, which is already compromised by edema and inflammation in patients with ALI/ARDS. Several 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 [197–200].

VII. Potential for combining exogenous surfactant with other therapies in ALI/ARDS

The foregoing discussion has focused on exogenous surfactant therapy as an individual intervention. However, even if extra-pulmonary pathology is absent or relatively minimal in patients with ALI/ARDS, the multifaceted pathophysiology of lung injury itself is still present. Individual pharmacologic agents such as exogenous surfactant may in fact mitigate their intended target of pathology, but a benefit to survival and other long-term clinical outcomes in patients may be obscured by remaining aspects of lung injury pathology. A large body of scientific research elucidating many of the mechanisms of pulmonary injury and inflammation now exists, and is continuing to expand rapidly. Such research has already identified multiple biological processes and pharmacologic agents that could potentially be used concurrently with exogenous surfactant to treat complementary targets in the pathophysiology of ALI/ARDS. Many agents when studied individually in cell or animal research on lung injury have shown measurable benefits, but have not been found to improve survival and other significant outcomes in patients with ALI/ARDS. Rational mechanism-based combination therapies that concurrently target different aspects of lung injury pathology may have more success in improving long-term patient outcomes, as reviewed in detail elsewhere [111, 201]. Combination therapies for ALI/ARDS could include not only pharmacological agents, but also multimodal strategies incorporating non-pharmacologic interventions such as different protocols or modes of mechanical ventilation or patient positioning.

Potential biological targets in addition to surfactant dysfunction in the acute exudative phase of ALI/ARDS include hypoperfusion and ventilation/perfusion mismatching, arterial

hypoxemia, edema, inflammation, oxidant injury, and injury to alveolar epithelial and capillary endothelial cells (Table 8). Agents and interventions targeting many of these abnormalities are discussed in other chapters in this issue of *Critical Care Clinics*, and many may have potential utility in combination therapy approaches with exogenous surfactant. Examples of pharmacologic agents in addition to exogenous surfactant that have been tested individually in patients with ALI/ARDS or sepsis include vasoactive agents such as inhaled nitric oxide(INO), almitrine, or prostacyclin [202–218]; β-2 agonists such as salbutamol to reduce edema [219–221], anti-coagulants like TFPI (tissue factor pathway inhibitor) and anti-thrombotic protein C (APC) [222–224]; anti-inflammatory antibodies or receptor antagonists such as anti-TNFα [225–228] and interleukin (IL)-1 receptor antagonist (IL-1Ra) [229, 230]; anti-inflammatory agents like pentoxifylline and corticosteroids [231–241]; and anti-oxidants like N-acetylcysteine [242–244] and superoxide dismutase [245, 246]. Non-pharmacologic interventions that could be utilized in combination therapies include modes or strategies of mechanical ventilation that enhance alveolar recruitment and minimize ventilator-induced lung injury [247–259]. Prone positioning can also be used to enhance alveolar recruitment and ventilation in patients with ALI/ARDS (e.g., [260]). These agents and interventions, and their potential utility in combination therapies for acute exudative ALI/ARDS are detailed more fully elsewhere [111, 201]. As one representative example, the possible benefit of concurrent use of exogenous surfactant therapy with INO is discussed briefly below.

Clinical studies have shown that INO alone improves arterial oxygenation and reduces pulmonary artery pressure in adults with ARDS [202–210] and in infants or children with acute respiratory failure [261–266]. The rationale for combination therapy with INO and exogenous surfactant is based on their complementary mechanisms of action in improving ventilation/perfusion matching and gas exchange. INO dilates the vasculature in ventilated lung units, while surfactant improves ventilation by decreasing surface tension and enhancing alveolar stability and recruitment. Exogenous surfactant therapy would theoretically increase the ventilated lung area accessible to INO, while the latter would increase the perfusion of these ventilated areas. Additive improvements in lung function from the simultaneous use of INO and exogenous surfactant have been demonstrated in premature surfactant-deficient lambs with congenital diaphragmatic hernia [267], as well as in animal models of ALI/ARDS [268–273]. A stepwise, multiple regression analysis of neonates with hypoxic respiratory failure being weaned from INO has demonstrated that therapeutic surfactant significantly enhanced oxygenation reserve [274]. Clinical benefits have been reported from exogenous surfactant therapy and INO in a small case series in full-term infants with severe acute respiratory failure [275]. These findings support more extensive study of combination therapy with surfactant and INO in ALI/ARDS. This is also the conclusion of a review of newborns < 5 days old and ≥ 35 weeks gestation diagnosed with hypoxemic respiratory failure (oxygenation index >15) from meconium aspiration, sepsis/pneumonia or persistent pulmonary hypertension in the eras preceding (1993–1994) and following (1996–1997) the simultaneous availability of high frequency oscillatory ventilation, INO and exogenous surfactant [276]. The simultaneous availability of these therapies was associated with a reduced percentage of infants requiring rescue therapy with ECMO (42.8% vs. 27.7%) that was not fully attributable to the reported efficacy of the individual agents alone [276]. The efficacy of INO has also been reported to be additive with those of PEEP [277] and patient prone positioning [278].

Developing and testing combination interventions for ALI/ARDS is challenging no matter what agents or specific treatments are involved. Controlled clinical trials are ultimately essential for defining the efficacy of any specific combination therapies in ALI/ARDS. However, the complexity, time, and cost associated with such clinical trials makes it particularly important also to make maximum use of laboratory studies in animal and cell models to evaluate a broader range of potential combination regimens so that clinical testing

can be focused on the most promising interventions. Because of the rapid pace of progress in understanding inflammation and lung injury at the molecular and cellular level, there is reason for optimism about the potential for eventually developing combination therapies able to effect substantial improvements in survival and other long term outcomes for patients (or targeted patient subgroups) with ALI/ARDS.

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

Exogenous surfactant therapy is a standard life-saving intervention for the prevention and treatment of NRDS in premature infants, and basic science and clinical evidence support strongly 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 well-documented to have become a standard intervention in many neonatal intensive care units. Surfactant therapy is also used routinely in infants and children with lung-injury related acute respiratory failure from pulmonary viral or bacterial infections (pneumonia). Controlled trials of exogenous surfactant therapy in children up to age 21 with ALI/ARDS have also shown significant benefits, with significant survival advantages in direct pulmonary forms of ALI/ARDS documented in the randomized controlled trial of Willson et al [21].

Current clinical evidence supporting the use of surfactant in adults with ALI/ARDS is less compelling than in infants and children. However, the surfactants that have been most extensively studied in adults with ARDS (Exosurf® and Survanta®) have known limitations in composition and activity compared to several other available preparations. Adult studies to date have also not focused on direct pulmonary forms of ALI/ARDS, 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., [279]), possibly as a result of better intrapulmonary drug distribution coupled with minimized ventilator-induced lung injury. Similar advantages might accompany early as opposed to later surfactant administration in patients with ALI/ARDS, if individuals who are at greater risk for progression to respiratory failure can be accurately identified nearer the start of their clinical course. Although it is challenging and expensive to examine surfactant therapy in controlled clinical trials, further studies of direct pulmonary forms of ALI/ARDS with the most active available exogenous surfactants delivered effectively to the alveoli are warranted based on current pathophysiological understanding and extensive biophysical and animal research.

An additional consideration for surfactant therapy in ALI/ARDS involves its use in combination with agents or interventions targeting other aspects of the complex pathophysiology of acute pulmonary injury. A combination therapy approach appears particularly relevant for adults with ALI/ARDS, where responses to exogenous surfactant have so far been disappointing. The use of multiple therapeutic agents or interventions based on a mechanistic rationale for synergy may significantly enhance outcomes in patients with complex inflammatory lung injury pathology. Examples of specific biological targets, pharmacologic agents, and other interventions that might be synergistic with exogenous surfactant in ALI/ARDS have been described in the section just preceding this summary. Given the known contributions of surfactant dysfunction in inflammatory lung injury, it seems likely that surfactant therapy alone or in combination with other agents will ultimately be applicable for at least some adult as well as pediatric patients with ALI/ARDS caused by direct forms of pulmonary injury.

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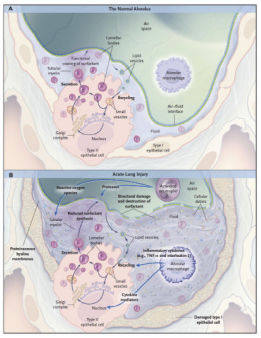

FIGURE 1. Surfactant production and recycling in the normal alveolus (Panel A) and changes in surfactant metabolism in acute pulmonary injury (Panel B) [283]

In the normal alveolus (Panel A), surfactant is synthesized and packaged into lamellar bodies in the cytoplasm of type II epithelial cells. The exocytotic lamellar body organelles secrete surfactant into the alveolar hypophase, where it forms tubular myelin and other active large lipid-protein aggregates. Surfactant lipids and proteins adsorb to the alveolar air-liquid interface as a highly-active film that lowers and varies surface tension during breathing. Surfactant activity is physiologically essential in reducing the work of breathing, stabilizing alveoli against collapse and over-distension, and lowering the hydrostatic driving force for pulmonary edema. In injured lungs (Panel B), multiple inflammatory cytokines and chemokines can influence the metabolism of alveolar surfactant (synthesis, secretion, reuptake, recycling) by altering type II pneumocyte function and responses (Panel B). Surfactant metabolism in type II cells can also be altered as a result of type I cell injury, since the former are stem cells for the alveolar epithelium. In addition, inflammation and permeability injury can lead to the presence of reactive species and other substances in the interstitium and alveoli that can interact chemically or physically with lung surfactant lipids and proteins. Examples of specific pathways by which the surface-active function of alveolar surfactant can be impaired during acute pulmonary injury are described further in Figure 2. TNF is tumor necrosis factor.

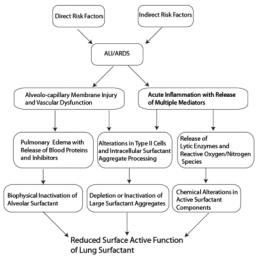

FIGURE 2. Causes of decreases in lung surfactant surface-active function during acute pulmonary injury (ALI/ARDS)

Although available amounts of surfactant may be decreased as a result of type II cell injury in some forms of ALI/ARDS, surfactant deficiency is typically much less prominent than surfactant dysfunction (reduced surface activity). Dysfunction of alveolar surfactant can result from several pathways in injured lungs, with one prominent mechanism being inactivation from biophysical interactions with inhibitor compounds like plasma/blood proteins or cellular lipids that enter the alveoli in edema fluid. Alveolar surfactant can also be chemically degraded or modified by substances present in the innate inflammatory response such as lytic enzymes (proteases, phospholipases) or reactive oxygen/nitrogen species. In addition, injury-induced depletion or compositional changes in large alveolar surfactant aggregates may lead to a decrease in overall surface-active function because such aggregates normally have the highest apoprotein content and surface activity. Modified from Reference [36, 37].

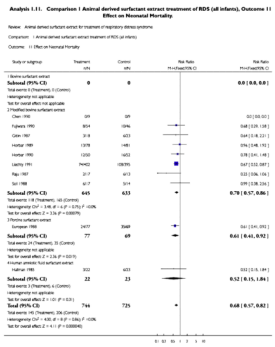

FIGURE 3. The effect of exogenous surfactant on mortality in infants with NRDS (adapted from[153])

The figure shows the results of meta-analyses of data on infant mortality from clinical trials of surfactant replacement therapy with modified bovine surfactant, porcine surfactant extract, and human amniotic fluid surfactant extract. Overall, treatment with animal-derived surfactant extracts significantly decreased the risk of neonatal mortality (typical relative risk 0.68, 95%CI 0.57, 0.82; typical risk difference −0.09, 95% CI −0.13, −0.05). The number of patients needed to be treated to prevent one neonatal death was 11 (95% CI 8, 20 Significant heterogeneity was not noted between the trials analyzed. Meta analysis also indicated that the subgroup of trials using modified bovine surfactant extract also had a significant decrease in the risk of neonatal mortality (typical relative risk 0.70, 95% CI 0.57, 0.86; typical risk difference −0.08, 95% CI −0.12, −0.03). In addition, the trial of porcine surfactant extract (European 1988) individually demonstrated a decrease in the risk of mortality (relative risk 0.61, 95% CI 0.41, 0.92).

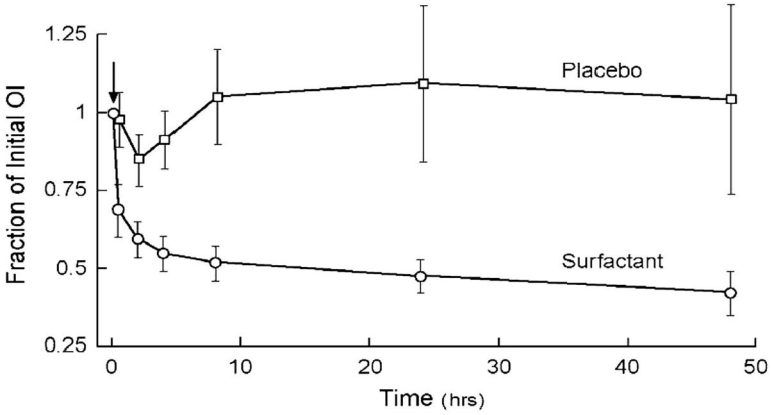

FIGURE 4. Improvements in oxygenation index (OI) after instillation of exogenous surfactant in children with ALI/ARDS [140]

Patients ranging in age from 1 day through 18 years in eight pediatric intensive care units were randomized to surfactant or control groups in the 1999 study of Willson et al [140]. 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 are Mean ± S.D. from Willson et al [140].

Table 1

Causes of neonatal respiratory distress syndrome (NRDS), clinical acute lung injury (ALI), and acute respiratory distress syndrome (ARDS).

Syndrome	Primary	Patient	Associated	Predisposing
NRDS	Surfactant-deficiency due to immature alveolar type II epithelial cells	Premature infants	Complications of prematurity	Premature birth
ARDS/ALI (Direct injury)	Direct injury to the lungs	Any age	Added pathology from the specific lung injury insult can also occur	Aspiration Pulmonary infection Lung contusion Near drowning Hyperoxia Smoke inhalation Other inhaled toxins Lung radiation
ARDS/ALI (Indirect injury)	Lung injury results from an extra-pulmonary insult and inflammation	Any age	SIRS, MODS, MOF, and less severe forms of multi-organ	Sepsis Hypovolemic shock Non-thoracic trauma Burn injury Pancreatitis

MODS: multiple organ dysfunction syndrome; MOF: multiple organ failure; SIRS: systemic inflammatory response syndrome. Table adapted from [37]. See text for discussion.

Table 2

Examples of injury-induced endogenous compounds that inhibit lung surfactant activity through physical or chemical interactions.

BIOPHYSICAL INHIBITORS
• Plasma and blood proteins (e.g., albumin, hemoglobin, fibrinogen, fibrin monomer)
• Cell membrane lipids
• Lysophospholipids
• Fluid free fatty acids
• Glycolipids and sphingolipids
• Meconium in term infants
CHEMICALLY-ACTING INHIBITORS
• Lytic enzymes (proteases, phospholipases)
• Reactive oxygen and nitrogen species (ROS, RNS)
• Antibodies to surfactant proteins

See text for literature citations and discussion.

Table 3

Animal models of acute pulmonary injury shown to respond to exogenous surfactant therapy *in vivo*.

Acid aspiration [80–82]
Meconium aspiration [83–86]
Anti-lung serum infusion [87]
Bacterial or endotoxin injury [88–93]
Pulmonary contusion [78]
Bilateral vagotomy [94]
Hyperoxic lung injury [95–99]
In vivo lung lavage with mechanical ventilation [100–105]
N-nitroso-N-methylurethane lung injury [106–108]
Viral pneumonia [109, 110]

See text for discussion.

Table 4

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)
	Novel lipid/peptide synthetic surfactants (e.g., Super Mini-B surfactants)

Curosurf ® (Chesi Farmaceutici; Dey Laboratories), Infasurf® (ONY, Inc; Forest Laboratories), and Survanta® (Abbott/Ross Labs) are FDA-approved in the USA. Exosurf® (Glaxo-Wellcome) is also FDA-approved, but is no longer used clinically. Surfaxin® (KL4, Discovery Labs) is under clinical evaluation. Specifically bioengineered synthetic lipid/peptide surfactants having the potential for even greater activity in ALI/ARDS are currently under development, including preparations containing novel phospholipase-resistant lipids plus highly-active peptides incorporating the most active sequences in human SP-B (e.g., Super Mini-B peptide [121]). Further details on the composition, activity, and inhibition resistance of clinical exogenous surfactants are reviewed elsewhere (e.g., [37, 201, 280, 281]). Table adapted from Refs [37, 281].

Table 5

Selected controlled and uncontrolled clinical studies reporting benefits of exogenous surfactant therapy in acute respiratory failure (ALI/ARDS).

Study	Patients (N)	Disease	Surfactant	Outcomes
Günther et al (B)[135]	Adults (27)	ARDS	Alveofact®	Improved surfactant function
Walmrath et al (B) [196]	Adults (10)	ARDS, sepsis	Alveofact®	Improved oxygenation
Spragg et al (B)[137]	Adults (6)	ARDS, multiple causes	Curosurf®	Improved oxygenation and biophysical function
Wiswell et al (B)[138]	Adults (12)	ARDS, multiple causes	Surfaxin®	Improved oxygenation
Amital et al (A)[282]	Adults (42)	Lung transplant	Infasurf®	Improved oxygenation, better graft function
Spragg et al[22]	Adults (40)	ARDS, multiple causes	Venticute®	Improved oxygenation, decreased IL-6 in BAL
Willson et al (A)[139, 140]	Children (29 & 42)	ARDS, multiple causes	Infasurf®	Improved oxygenation
Willson et al (A)[21]	Children (152)	ARDS, multiple causes	Infasurf®	Improved survival and improved ventilation
Lopez-Herce et al(B)[141]	Children (20)	ARDS + post-op cardiac	Curosurf®	Improved oxygenation
Hermon et al(B)[142]	Children (19)	ARDS + post-op cardiac	Curosurf® or Alveofact®	Improved oxygenation
Herting et al(B)[143]	Children (8)	Pneumonia	Curosurf®	Improved oxygenation
Moller et al (A)[159]	Children (35)	ARDS, multiple causes	Alveofact	Improved oxygenation
Auten et al (B)[144]	Infants (14)	MAS or Pneumonia	Infasurf® (CLSE)	Improved oxygenation
Lotze et al (A)[145, 146]	Infants (28 & 328)	ECMO, multiple indications	Survanta®	Improved oxygenation, decreased ECMO
Khammash et al (B)	[147] Infants (20)	MAS	bLES®	Improved oxygenation in 75% of patients
Findlay et al (A) [148]	Infants (40)	MAS	Survanta®	Improved oxygenation, decreased pneumothorax and mechanical ventilation
Luchetti(A) et al [149, 150]	Infants (20 & 40)	RSV bronchiolitis	Curosurf®	Improved oxygenation

MAS: meconium aspiration syndrome; RSV: Respiratory syncytial virus. The tabulated studies of Willson et al [21, 140], Findlay et al [148], Moller et al [159], Lotze et al [145, 146], Luchetti et al [149, 150], and Amital et al [282] were controlled trials(A), while the remaining studies were uncontrolled treatment trials(B) as detailed in the text. Table adapted from [280].

Table 6

Clinical outcomes from the controlled 2005 study of Willson et al [21] on surfactant therapy in pediatric patients up to age 21 with ALI/ARDS.

	Infasurf® (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 conventional mechanical ventilation (CMV) had more than one non-conventional therapy (ECMO, iNO, or HFOV);

#Costs are given in thousands of dollars. Abbreviations: ECMO = extracorporeal membrane oxygenation; HFOV = high frequency oscillatory ventilation; iNO = inhaled nitric oxide; LOS = length of stay. In addition to improving mortality and reducing the percentage of patients who failed CMV, the table, instilled Infasurf® (70 mg/kg) also significantly improved oxygenation index compared to placebo (P=0.01) in analogy with findings an earlier trial by the same group shown in Figure 1. Data are from Willson et al [21].

Table 7

Efficacy of exogenous surfactant therapy in direct and indirect lung injury in the controlled 2005 study of Willson et al [21] 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

Treatment was with Infasurf® (Calfactant) at a dose of 70 mg/kg body weight [21]. 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 therapy is seen confined to patients with direct pulmonary forms of ALI/ARDS. See text for details.

TABLE 8

Selected biological targets for pharmacotherapy that can be used in addition to surfactant therapy in ALI/ARDS.

Target	Contributing abnormalities/processes	Selected desired outcomes
Hypoperfusion and ventilation/perfusion mismatching	Hypoxic vasoconstriction Inappropriate vasodilation Microvascular occlusion	Treat with agents to vasodilate ventilated lung regions, vasoconstrict non-ventilated lung regions, and reduce microvascular thrombosis
Surfactant dysfunction or deficiency	Physicochemical inhibitors of surfactant in edema or inflammation, or injury to type II pneumocytes	Deliver exogenous surfactant to reverse surfactant dysfunction/deficiency to improve alveolar stability, reduce edema, and normalize P-V mechanics
Over-exuberant inflammation	Activation/recruitment of inflammatory leukocytes and over-exuberant production of inflammatory mediators	Deliver agents to remove or deplete activated neutrophils, macrophages or other leukocytes, or to block the effects of specific inflammatory mediators
Arterial hypoxemia, alveolar and interstitial edema	Decreased gas exchange, increased permeability, and decreased resorptive capacity of the alveolocapillary membrane	Delivery of agents to reduce edema coupled with mechanical ventilation strategies to raise arterial oxygenation without increasing permeability injury
Death/injury of cells in airways and alveolocapillary membrane	Loss of normal ciliated airway epithelium alveolar type I cells, and microvascular endothelial cells	Reduce cell death and the severity of cellular injury by delivering antioxidants or other cell- protective agents

Examples of pharmacologic targets that could potentially be targeted in combination therapies with exogenous surfactant (also listed) in the acute exudative phase of ALI/ARDS are summarized. A variety of additional targets in the later fibroproliferative/fibrotic phase of ALI/ARDS also exist. Adapted from [111].