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Research review paper

Clinical, technological, and economic issues associated with developing new lung surfactant therapeutics

Hyun Chang Kim, You-Yeon Won*

School of Chemical Engineering, Purdue University, West Lafayette, IN 47907, United States

ABSTRACT

Discovery of lung surfactant deficiency as a main cause of neonatal respiratory distress syndrome (NRDS) has influenced a steep increase in lung surfactant research. Although this has yielded impactful scientific discoveries, much of the basic research on lung surfactants has failed to translate into clinical practices. This is attributed to insufficient information covering the entire lung surfactant ecosystem, from the basic science to economics surrounding the development and clinical practices. In this manuscript, developments related to improving therapeutic lung surfactant as well as the degree of unmet need are analyzed from both technical and economic perspectives. Two potential opportunities are emphasized: (1) aerosolized lung surfactants to treat NRDS infants, and (2) synthetic lung surfactants for acute respiratory distress syndrome (ARDS) patients. Each has a modestly projected US market size of $120 million and $4 billion, well enough to make up for the high development costs associated with investigational drug development. Both opportunities have been pursued in the past, but to date these attempts have met with no success mainly due to technical limitations. With the recent advancements in both fields, technology improvements have created opportunities to solve both decades-old problems.

1. Introduction

Lung surfactant is a great example of how knowledge in basic science can translate into a life-saving product. Without lung surfactants our lungs would disproportionately collapse due to imbalance in lung alveoli pressures. The remarkable physicochemical behaviors of lung surfactants have been well studied for the past few decades. However, today there still lies a gap in the available literature necessary to link the clinical practices, basic science, and the pharmacoeconomics of therapeutic lung surfactants. This article contains an analysis of the entire therapeutic lung surfactant ecosystem and identifies the requirements for the next generation of therapeutic lung surfactants. We would like to note that readers interested in basic biology, biochemistry and physiology of lung surfactants should consult other sources such as the references listed in References (Notter, 2000; Lachmann, 1989; Nag, 2005; Robertson and Taeusch, 1995; Khubchandani and Snyder, 2001; Kingma and Whitsett, 2006; Sato et al., 2010).

2. The US lung surfactant market is currently saturated with three well-established products

In current clinical practices, therapeutic lung surfactant indications are limited to neonatal respiratory distress syndrome (NRDS) and meconium aspiration syndrome (MAS). The two indications are both infant-related, but differ in terms of gestation period and mechanism. NRDS is caused by lung surfactant deficiency in premature infants, whereas MAS is caused by lung surfactant deactivation in post-term infants when they aspirate meconium stained amniotic fluids. The prevalence for NRDS is 10 out of 1000 infants, and the prevalence for MAS is 0.43 out of 1000 infants (Dargaville and Copnell, 2006). The higher prevalence of NRDS over MAS has led to NRDS being the indication of focus during the development history of therapeutic lung surfactants. In this section, NRDS is discussed first, while MAS is revisited in a later section along with acute respiratory distress syndrome (ARDS).

When infants are born preterm, without the full production of lung surfactants, the lungs are collapsed and are unable to provide sufficient levels of oxygen. To address this issue, the first approach was to increase the level of oxygen delivered to the infant's lungs using ventilators. In the late 1960s mechanical ventilators improved substantially, and the infant survival rates increased from 23% to 70% (Cumarasamy et al., 1973). Another treatment that helped to improve the infant survival rates from NRDS was antenatal corticosteroid treatments. Infants' mothers treated with corticosteroid 24 h before giving birth were shown to reduce the infant's chance of developing NRDS by 50% (Liggins and Howie, 1972; Crowley, 1995).

* Corresponding author.
E-mail address: yywon@ecn.purdue.edu (Y.-Y. Won).

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Table 1
Comparison of the three animal extracted lung surfactant therapies marketed in the US. More detailed information regarding these products can be found in References (Notter, 2000; Zhang et al., 2011; Curosurf.com, 2018).

	Curosurf (Chiesi)	Infasurf (ONY)	Survanta (AbbVie)
Source	Porcine lung mince	Calf lung lavage	Bovine lung mince
Phospholipid concentration (mg/ml)	76	35	25
SP-B (mg/ml)	0.45	0.26	0.01
SP-C (μg/μM phospholipid)	5.0–11.6	8.1	1.0–20.0
Cholesterol (mg/ml)	0	2.0–3.0	< 0.06
Dose volume (ml/kg)[a]	2.5	3	4
Surfactant dose (mg/kg)	200	105	100

[a] The dose volume is for the first initial recommended dose. Recommended additional doses are: up to 2 additional doses (total 3 doses) of 1.25 ml/kg per dose for Curosurf with 12 h intervals, up to 2 additional doses of 3 ml/kg per dose for Infasurf with 12 h intervals, and up to 3 additional doses of 4 ml/kg per dose for Survanta with at least 6 h intervals in the first 48 h after birth.

In the 1950s, Avery and Mead discovered the root cause of NRDS to be from lung surfactant deficiency; (Avery and Mead, 1959) this finding was the start of a new wave of research on lung surfactants, both basic and clinical. By the 1990s, therapeutic lung surfactants extracted from animals became available in clinical practices. This so-called surfactant replacement therapy using animal extracted lung surfactants has led to decreasing the NRDS-related mortality rates down to < 2%. Over the years different animal extracted lung surfactants entered the market with variations in their formulation preparation. In the US, there are currently three animal extracted lung surfactants; Survanta (AbbVie), Curosurf (Chiesi), and Infasurf (ONY), with Survanta being the first to enter the US market followed by Infasurf and then Curosurf. A detailed comparison of the three products is shown in Table 1.

In addition to the different compositions of the therapeutic lung surfactants, the business strategies used for the three products are also different. Chiesi and ONY are small sized pharmaceutical companies, and sales of therapeutic lung surfactants are their primary focus, whereas AbbVie, being a large sized pharmaceutical company, utilizes Survanta as a doorway to access the hospital formularies to promote their infant nutrition products (NSF I-Corps Interviews, 2017). This strategy has kept the price of Survanta low, $600–800 per treatment, despite it being a life-saving product (NSF I-Corps Interviews, 2017). Comparatively, other life-saving products such as cancer drugs are priced around $30,000 per treatment (Siddiqui and Rajkumar, 2012). For small pharmaceutical companies such as Chiesi and ONY, the low price standard set by AbbVie limits their pricing tactics. When Infasurf and Curosurf first entered the US market they were offered at discount prices of 15% and 30% off, respectively (NSF I-Corps Interviews, 2017). Chiesi's response strategy to AbbVie was to use aggressive marketing to capture the majority market share (NSF I-Corps Interviews, 2017).

To acquire the majority of the market share, Chiesi promotes that Curosurf achieves higher performance when compared to Survanta and Infasurf. Dissecting this claim, Curosurf has a lower dose volume of 2.5 ml/kg, which is claimed to be advantageous in reducing the risk of blockage during the intratracheal instillation procedures (Wiseman and Bryson, 1994). However, a lower liquid dose can limit even distribution of the lung surfactants and reduce the overall amount of active ingredient delivered to the deep lungs (Halpern et al., 1998; Filoche et al., 2015). Chiesi has supported many research studies and clinical trials directly comparing Curosurf to other products to acquire evidence of the product's superiority (Speer et al., 1995; Ramanathan et al., 2013; Cogo et al., 2009). From a clinical and scientific perspective, controversies still remain on which formulation truly is most effective, but from the sales data, Chiesi was successful in capturing a majority of the market share as shown in Fig. 1. Interestingly, most of the market share gains made by Curosurf have come from Survanta's market share. This is speculated to be due to the combination of AbbVie's low focus on marketing Survanta and the product's extremely low SP-B level.

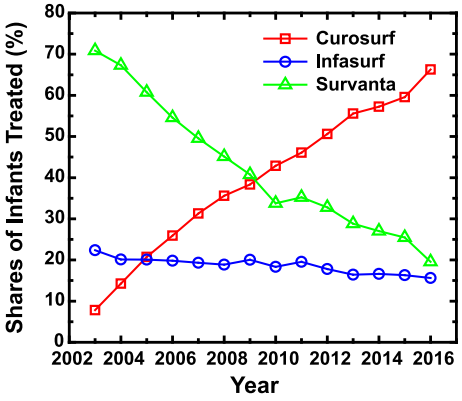

Fig. 1. Shares of infants treated with Curosurf, Infasurf, and Survanta in the US from 2003 to 2016. Data were extracted from IMS lung surfactant market purchases from May 2004 to December 2012 and Symphony SHA lung surfactant purchases from January 2013 to September 2016.

3. For investigational new drug development, the market size needs to be in the hundreds-of-million-dollar range to recover the high development cost

As in any other field, development priority is given to products that have a significant clinical impact and can overcome the costs associated with development. Typically, the development phase is expected to take around 10 years to complete with the majority of costs being associated with required clinical trials that average $33.4 million (Martin et al., 2017). From a clinical perspective, there is still room for improvement in the current lung surfactant formulation. One example is that the clinical outcomes in terms of NRDS-related mortality for low birth weight infants are significantly different depending on the product used. A retrospective observational cohort analysis performed by Ramanathan et al. shows a mortality rate of 11.72% for 500–749 g birth weight infants treated with Curosurf compared to 17.39% for Infasurf and 20.67% for Survanta (Ramanathan et al., 2013). Another example that shows the need for further formulation optimization is the result of a lower infant mortality rate when treated with a higher dose of Curosurf (200 mg/kg) compared to a lower dose of Curosurf (100 mg/kg) (Ramanathan et al., 2004). In a side-by-side comparison clinical trial of Curosurf versus Survanta (N = 293), the 200 mg/kg (= 80 mg/ml × 2.5 ml/kg) dose of Curosurf exhibited a significantly lower mortality rate of 3.0% compared to 6.25% for 100 mg/kg (= 80 mg/ml × 1.25 ml/kg) Curosurf and 8.16% for 100 mg/kg (= 25 mg/ml × 4 ml/kg) Survanta (Ramanathan et al., 2004). In a different clinical trial, the efficacies of 120 mg/kg (= 30 mg/ml × 4 ml/kg) and 60 mg/kg (= 30 mg/ml × 2 ml/kg) doses of Surfactant-TA (Tokyo Tanabe) were compared (N = 46) (Konishi et al., 1988). Although mortality rates were comparable between the two dose levels, the incidences of intraventicular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD) were significantly less in the higher dose group. These clinical trial results suggest that improving the current lung surfactant formulation could result in saving more premature infants from NRDS-related conditions as well as complications that typically arise down the road. Unfortunately, the question, which lung surfactant composition at what dose level yields the best clinical efficacy remains unanswered; a conclusion could only be drawn when results from a large-scale randomized clinical trial involving all products become available. Thus far, clinical investigations comparing different products mainly involved either side-by-side comparisons of two products (e.g., Curosurf vs.

Survanta (Speer et al., 1995; Ramanathan et al., 2004; Ann Malloy et al., 2005), Infasurf vs. Survanta (Bloom et al., 1997), and Alveofact vs. Survanta (Griese et al., 1995)) or retrospective analyses of data from previous medical records (e.g., Surfactant-TA vs. Infasurf vs. Curosurf (Jeon et al., 2015), and Survanta vs. Infasurf vs. Survanta (Trembath et al., 2013)).

Generally, a significant clinical impact translates into a high return of investment (ROI) for pharmaceutical products, offsetting the costs associated with development. However, an important factor that also needs to be considered is the patient pool size. In 2015, 3.98 million infants were born in the US (Hamilton et al., 2016). Out of the 3.98 million about 321,000 infants (8.07%) were born with low body weight (< 2500 g), which can be corresponded to being born before the 36th week of gestation (Hamilton et al., 2016). Out of the 321,000 premature infants about 10% develops RDS (32,100 infants). A higher prevalence rate of over 80% if infants are born before 24 weeks, and < 5% prevalence for infants born between 28 and 32 weeks (St. Clair et al., 2008; Donn and Sinha, 2016). From 2010 IMS sales data, the annual US sales of lung surfactants was $73 million. Out of the $73 million, approximately $4 million are estimated to be for MAS infants, and $69 million for NRDS infants. Considering each lung surfactant vial is single-use, and the average cost is $600, about 115,000 lung surfactant doses were administered annually to NRDS infants. This number is high compared to the annual US prevalence of 32,100 NRDS infants, even when multiple dose treatments for ~40% RDS infants are considered (Guardia et al., 2012). This surplus lung surfactant consumption is due to prophylactic treatment protocols in some hospital systems (Soll and Morley, 2001). From an economic perspective, this is not a favorable market to enter with a new product, because the market size is small and already in its fully matured state. Unless a new drug is given a premium price, the lung surfactant market size for the NRDS indication will continue to be around $69 million, making recovery of development costs improbable.

Premium pricing for a new lung surfactant can be employed under two scenarios. One is the new lung surfactant having a significantly reduced mortality rate compared to existing products. However, the current mortality rate of NRDS infants born during 28–32 weeks of gestation, which make up over 90% of the premature infant population, is ~2% (Ramanathan et al., 2013; St. Clair et al., 2008). This 2% mortality rate includes NRDS infants who also have other complications (i.e., hemorrhage, infection, immaturity, etc.), suggesting that the cause of mortality may be due to other factors rather than solely from lung surfactant deficiency. Although the complete elimination of NRDS-related mortality is the ultimate goal, at this stage, there is only room for marginal improvement with regard to reducing surfactant deficiency-related mortality beyond what has already been accomplished in this fully matured market. Thus, acquiring premium pricing via this scenario is unlikely for a new lung surfactant.

A better strategy for achieving premium pricing is to develop a new lung surfactant that does not depend on mechanical ventilation, which currently contributes to higher hospitalization costs for patients and imposes risks of future complications. When therapeutic lung surfactants were first developed in 1990s, they were considered an expensive drug. To this day, there is consensus that this is still the case. However, the drug itself is not of high cost; it is the expense associated with subsequent mechanical ventilation treatment estimated at $967 per day (the total hospitalization cost is $2692 per day) that makes surfactant replacement therapy (SRT) a costly treatment (NSF I-Corps Interviews, 2017; Guardia et al., 2012). The average duration under mechanical ventilation following surfactant administration is 2 days, while additional surfactant administration extends this duration to 7–8 days (Trembath et al., 2013; Guardia et al., 2012). Furthermore, in addition to the expensive mechanical ventilation costs, prolonged exposure to mechanical ventilation increases the infant's risk of developing bronchopulmonary dysplasia (BPD). BPD is a chronic lung disease, for which, in the infant stage alone, the treatment cost can be around $37,739 (Johnson et al., 2013). Despite its clinical and economic downsides, intubating the infant to a mechanical ventilator and administrating lung surfactant via a rapid bolus injection remains the most effective delivery method. Methods such as INSURE (Intubation-SURfactant-Extubation) which involves brief intubation for surfactant instillation and extubating to CPAP (Continuous Positive Airway Pressure) from mechanical ventilation have shown indications of clinical benefits (Verder et al., 1999), but concrete clinical data are still pending. Similarly, the LISA (Less Invasive Surfactant Administration) method (using a very thin catheter compared to the conventional 5 French end-hole catheter) has been reported to improve clinical outcomes (Lau et al., 2017). However, these claims have yet to be validated in large-scale clinical trials.

An alternative delivery method for therapeutic lung surfactants that does not rely on mechanical ventilation is through nebulization. A nebulizer can be connected to a CPAP system to provide both SRT and breathing support to the infant, but this requires lungs surfactant in an aerosol form for delivery. One barrier in developing an aerosolized lung surfactant has to do with the property of surfactants to form stable foams that cannot be effectively delivered using the conventional nebulizer technology (NSF I-Corps Interviews, 2017). This stems from such characteristics of lung surfactants as low surface tension, low permeability and high viscosity that make them prone to produce stable foams. Recently, with improved vibrating mesh type nebulizers, Windtree Therapeutics (previously, Discovery Laboratories) has reported success in aerosolizing their synthetic peptide(KL4)-based lung surfactant (Aerosurf) (Donn and Sinha, 2008). However, in their Phase 2b clinical trial involving 221 premature infants born between 28 and 32 weeks of gestation, Aerosurf delivered using CPAP was shown to exhibit a similar level of efficacy compared to the CPAP only control (Windtree Therapeutics, 2017). Windtree Therapeutics commented that the disappointing results were due to frequent interruptions of the treatment for replacements of disposable filter cartridges (Windtree Therapeutics, 2017). In fact, for infants that did not have frequent treatment interruptions (N = 45), Aerosurf/CPAP-treated infants exhibited a lower CPAP failure rate of 31% compared to 44% in the control CPAP group (Windtree Therapeutics, 2017). Successful aerosolization of lung surfactant has yet to be achieved, but the technology is steadily improving and may one day provide a less-invasive delivery alternative for SRT (Donn and Sinha, 2008; Hutten et al., 2015; Walther et al., 2014; Finer et al., 2010). Due to its non-invasiveness, aerosol delivery would significantly expand the utility of lung surfactant in prophylactic therapy, i.e., in high risk groups prior to (full) development of disease; this applies to both NRDS and ARDS situations, and a market potential analysis for NRDS aerosol therapy is provided in the next paragraph. On the other hand, it should also be pointed out that our argument that there is a need for a surfactant therapy that does not depend on mechanical ventilation does not mean that it is the surfactant therapy itself that primarily necessitates the mechanical ventilation; it is the patient's lung function that determines that requirement. In fact, in many NRDS cases, and certainly for therapy of ARDS (further discussed later), one of the potential positive outcomes of surfactant use is its ability to wean patients off ventilator support. The trend to provide surfactant to patients without mechanical ventilation would certainly be useful, but this may only be relevant to a subpopulation of patients; patients with severe lung dysfunction will still have to rely on mechanical ventilation.

Another benefit of aerosolized lung surfactant is the expansion of treatment to a wider range of infants. Annually about 265,000 premature infants are born in the body weight group of 1500–2500 g (during 31–36 weeks of gestation) (Gleason and Devaskar, 2011). Most of these infants exhibit only mild NRDS symptoms and do not receive therapeutic lung surfactant treatments to avoid additional costs and potential future complications associated with intubation (such as bronchopulmonary dysplasia (BPD), bruising, etc. (NSF I-Corps Interviews, 2017; Windtree Therapeutics, 2017)). Instead, they are

treated only with CPAP for breathing support, with a hope that the infant will stabilize on its own. Therapeutic lung surfactants could help infants breathe while under CPAP support, but as mentioned above, therapeutic lung surfactants are not administered, because the cost of intubation outweighs the benefit from lung surfactant treatment. Aerosol delivery of lung surfactants would allow these infants to receive therapeutic lung surfactant without intubation. This competitive advantage creates an exclusive submarket of 265,000 premature infants that could potentially benefit from the combined aerosolized lung surfactant and CPAP treatment. Not to mention the potential premium pricing from clinical benefits and hospitalization cost savings, if an aerosolized lung surfactant is priced at the same level as current therapeutic lung surfactants (i.e., on average $600 per vial) and a treatment adoption rate of 75% is assumed, this would result in an additional $120 million US lung surfactant market. It should be pointed out that although there are many benefits from aerosolized lung surfactants, the bolus delivery method will not be completely renounced. A typical bolus delivery method only takes a few minutes to complete, whereas aerosol delivery requires 25–50 min (Windtree Therapeutics, 2017). For extremely severe NRDS infants immediately needing therapeutic lung surfactants, the bolus delivery would remain the best option. Thus, should aerosol delivery be successful and adopted into clinical practices, the already existing $73 million US lung surfactant market centered around bolus instillation will decrease, but will not be completely replaced by aerosolized lung surfactants.

Another business strategy that needs to be considered is to target the global market. Currently, therapeutic lung surfactant sales are highly focused in developed countries. According to 2010 IMS sales figures, annual sales by region were as follows: US $73 million, Europe $61 million, Japan $17 million, South Korea $5 million, and the rest of the world $50 million (total $206 million globally). Not considering discounted prices of therapeutic lung surfactants in such countries as India, China, Pakistan, and Iran (Vidyasagar et al., 2011; Najafian et al., 2016; Sankar et al., 2016), but instead using US prices as a benchmark, in the scenario of a saturated global market, the global market size for therapeutic lung surfactants is $2.41 billion. This suggests that only 8.5% of the global population has access to therapeutic lung surfactant. There is still a plenty of room for growth in the global market, especially in emerging economies such as Brazil, Russia, India, China, and Mexico. Establishing sales in these countries would be beneficial from both clinical and business perspectives. For low resource countries, although the population that can benefit from therapeutic lung surfactants is large, using therapeutic lung surfactants is not recommended unless adequate neonatal care facilities are available. Therapeutic lung surfactant is only effective when ventilator support is provided. Power outage or malfunctioning of a mechanical ventilator would negate benefits of lung surfactant and increase mortality rates of infants treated with lung surfactants in areas where such problems are frequent.

4. Although therapeutic lung surfactant is shown to be effective in treating infants and children with ARDS, it is currently used only for treatment of a specific subgroup of ARDS infants (infants with MAS)

NRDS lung surfactant therapeutics have not been successful in treating ARDS. ARDS is different from NRDS in that respiratory distress originates from deactivation (not deficiency) of lung surfactants, caused by inflammation and permeation of the lungs. ARDS is typically caused by direct lung injury such as aspiration, infection, trauma or surgery, or by indirect injury such as sepsis or hypovolemic shock. Achieving full recovery from ARDS involves sustaining the patient's adequate breathing, while simultaneously treating the underlying cause. Therefore, for the treatment of ARDS, the efficacy of therapeutic lung surfactants should not be solely determined from mortality rates.

In ADRS treatment decisions, the patient's age is an important factor. Parameters for treatment of adult ARDS patients cannot simply be scaled down for treatment of children or infants, and vice versa. An ARDS type common in post-term and term infants is meconium aspiration syndrome (MAS). Aspiration of meconium causes airway obstruction, inflammation, and lung surfactant deactivation. Therapeutic lung surfactant has been shown to be effective in treating MAS. MAS infants treated with SRT exhibited improved oxygenation, shortened ventilation duration, shortened hospitalization, and reduced duration and better outcome of extracorporeal membrane oxygenation (ECMO) support (after SRT, some infants did not even require ECMO support). A difference between NRDS and MAS treatment protocols is that MAS infants are typically given maximum doses of therapeutic lung surfactants (e.g., 4 doses of 100 mg/kg Survanta), unless interrupted due to ECMO treatment (Lotze et al., 1998; Findlay et al., 1996; Khammash et al., 1993). This is consistent with in vitro experiments showing that deactivated lung surfactants were recovered after addition of excess lung surfactants (Stenger and Zasadzinski, 2007). In infants, other types of ARDS such as infection-induced ARDS have also been successfully treated with SRT (Tibby et al., 2000; Luchetti et al., 2002).

In children, ARDS can be caused by pneumonia, aspiration, sepsis, infection, accident trauma, etc. In a randomized clinical trial involving 42 patients, a group treated with 115 mg/kg Infasurf showed improved oxygenation, achieved earlier extubation from ventilation by 4.2 days, and required shorter stays in pediatric ICUs by 6 days (Willson et al., 1999). However, there were no significant differences in overall mortality rates between treatment and control groups (Willson et al., 1999). In a different clinical trial on 35 patients, the treatment group receiving 100 mg/kg Alveofact (Boehringer-Ingelheim) exhibited improvements in oxygenation (Möller et al., 2003). In this study, a significantly lower mortality rate of 55% was observed for the Alveofact-treated group relative to 80% for the control group (Möller et al., 2003). In a larger clinical trial involving 152 patients with a mean age of 7 years, the treatment group receiving 2 doses of 115 mg/kg Infasurf exhibited improved oxygenation and a reduced mortality rate (19.5%) compared to control (36.0%) (Willson et al., 2005).

5. Treating adult ARDS patients with NRDS lung surfactant therapeutics has been unsuccessful to date

One of the first clinical trials conducted to test the efficacy of therapeutic lung surfactant for adult ARDS patients was that using aerosolized Exosurf (Glaxo Wellcome) in 725 sepsis-induced ARDS adult patients (Anzueto et al., 1996). The result was disappointing with no clinical benefits observed in this patient group. However, this clinical trial was later criticized for (i) the selection of ARDS patients with indirect lung injury (sepsis), (ii) the use of Exosurf as the therapeutic of choice, and (iii) the aerosol delivery method (which has not yet been validated as an effective lung surfactant delivery method) (NSF I-Corps Interviews, 2017; Willson et al., 2015; Spragg et al., 2011; Baudouin et al., 2004). In a different clinical trial, 43 sepsis-induced ARDS adult patients were treated with varying doses of Survanta (50 mg/kg per dose up to 8 doses, 100 mg/kg per dose up to 4 doses, and 100 mg/kg per dose up to 8 doses) (Gregory et al., 1997). Interestingly, an improvement in mortality rate was observed for the high dose groups (18.8% for 100 mg/kg up to 4 doses, and 10.5% for 100 mg/kg up to 8 doses) compared to the lowest dose and control groups (50.0% for 50 mg/kg up to 4 doses, and 43.8% for control). Consequently, larger clinical trials were initiated to test efficacy of various lung surfactants: Venticute (Altana Pharma, two clinical trials with N = 448 (Spragg et al., 2004) and N = 843 (Spragg et al., 2011)), HL10 (LEO Pharmaceutical, N = 418) (Kesecioglu et al., 2009), and Infasurf (N = 308) (Willson et al., 2015). Details of these four clinical trials are summarized in Table 2.

Since the clinical trial of aerosolized Exosurf (Anzueto et al. (1996)) (Anzueto et al., 1996), the clinical trial of Venticute administered via bolus injection (Spragg et al. (2004)) (Spragg et al., 2004) was the next

Table 2
Comparison of four large-scale clinical trials on the efficacy of SRT in adult ARDS patients.

	Spragg et al. 2004 (N = 448) (Spragg et al., 2004)	Spragg et al. 2011 (N = 843) (Spragg et al., 2011)	Willson et al. 2015 (N = 308) (Willson et al., 2015)	Kesecioglu et al. 2009 (N = 418) (Kesecioglu et al., 2009)
Product name	Venticute	Venticute	Infasurf	HL 10
Mean patient age	53.2	57.0	54.5	57.3
Primary diagnosis (%)[a]	Sepsis (57), Pneumonia (Anzueto et al., 1996), Trauma/surgery (Gleason and Devaskar, 2011), Aspiration (Wiseman and Bryson, 1994), others (Gleason and Devaskar, 2011)	Aspiration (Hamilton et al., 2016), Pneumonia (86)	Viral- (Donn and Sinha, 2008), Bacterial- (Willson et al., 2005), Aspiration (Donn and Sinha, 2008), Pneumonia and others (Wiseman and Bryson, 1994)	Sepsis (Willson et al., 2015), Pneumonia (Gregory et al., 1997), Shock (NSF I-Corps Interviews, 2017), Trauma (Liggins and Howie, 1972), Others (Halpern et al., 1998)
Phospholipid concentration (mg/ml)	50	50	60	50
Instillation volume (ml/kg)	1	1	~1[b]	4
Dose (mg/kg)	50	50	~150	200
Dose frequency	At 4-h intervals	At 6, 12, 24, 36, 48, 72 and 96 h after initial dose	At 12-h intervals if improvement criteria are met	At 3 and 12 h after initial dose
Maximum dose	4	8	N/A	3

[a] Contained patients with multiple symptoms.
[b] An adult body height to weight ratio of 2.1 cm/kg was used to convert the 0.5 ml/cm instillation volume used in the study to the units of ml/kg.

large-scale study that tested the efficacy of lung surfactant in adult ARDS patients. In the latter study, a slight improvement in oxygenation was observed in the Venticute-treated group, but the treatment did not lead to improved survival or a reduction in ventilation-free days compared to control. However, in a post hoc analysis, the mortality rate following surfactant treatment was estimated to be 30% for ARDS patients with direct lung injury (such as pneumonia or aspiration) (225 patients), which was lower than 37% for the control group. Based on these results, a follow up clinical trial (Spragg et al. (2011)) was carried out to test only in ARDS patients with direct lung injury as the underlying cause (Spragg et al., 2011). In this study, the clinical benefits observed in the previous study were not reproduced. The mortality rates, the numbers of ventilation free days, and oxygenation levels were all indistinguishable between treatment vs. control groups. These results were attributed to the possibility that the surfactants used were demulsified, and they were also deactivated by fibrinogen (Spragg et al., 2011). In a next clinical trial by Willson et al., 2015, the well-known product, Infasurf, was tested. In this study, the same type of ARDS patients (those with direct lung injury) were recruited, but the treatment did not produce a significant clinical cure. The reason for this result was suggested to be inappropriate Infasurf dose levels. Infasurf was concentrated to 60 mg/ml, and the instillation volume was lowered to 1 ml/kg; for NRDS infants, a surfactant concentration of 35 mg/ml and an instillation volume of 3 ml/kg are typically used. This high concentration/low volume instillation strategy was intended to minimize liquid volume injected into ARDS patient's lungs, where the lungs are already flooded with fluids. However, the authors commented that this might have been the cause of the poor outcome, considering that in NRDS infants, a higher liquid volume has resulted in a better treatment outcome (Willson et al., 2015). It should be noted that in the two clinical trials by (Spragg et al., 2004, 2011), the same low instillation volume (1 ml/kg) was used, which, therefore, could have also contributed to the disappointing results.

In the clinical trial of HL 10 by Kesecioglu et al. (2009) (Kesecioglu et al., 2009), the unsuccessful outcome cannot be associated with inappropriate surfactant dosing. This study used an appropriate phospholipid concentration of 50 mg/ml and a sufficient instillation volume of 4 ml/kg. However, no clinical benefits were observed in the treatment group, even in direct lung injury sub-populations. This clinical trial was, in fact, terminated prematurely due to higher mortality rates for treated patients (28.8%) than the untreated (24.5%). A possible argument can be made regarding the surfactant compound. HL 10 is freeze-dried natural surfactant isolated from pig lungs with 90–95% phospholipids and 1–2% SP-B and SP-C (Kesecioglu et al., 2009). Further analysis of this drug is impossible because the production of HL 10 has been discontinued after the clinical trial. The closest available analogue to HL 10 is Curosurf, which is also a procine lung extract. Assuming that this analogy is valid, two arguments can be made to explain the result of the clinical trial: deactivation, and concentration. An in vitro study has shown that relative to other lung surfactants (those derived from cows), Curosurf is most susceptible to deactivation by serum proteins such as fibrinogen, haemoglobin, or albumin (Seeger et al., 1993). Thus, HL 10 may not be the best choice for treating ARDS (Willson and Thomas, 2010). The 50 mg/ml surfactant concentration of HL 10 is higher than those of the bovine/calf products (25 mg/ml for Survanta, and 35 mg/ml for Infasurf), but it is lower than the surfactant concentration of Curosurf (76 mg/ml); the 50 mg/ml surfactant concentration of HL 10 might have been too low for producing therapeutic effects. Some (lung surfactant advocates) favor the view that choosing HL 10 was the root cause of the unsuccessful result (Willson and Thomas, 2010). Others speculate that the improved oxygenation observed in the study by Spragg et al. 2004 might have been an anomalous result (NSF I-Corps Interviews, 2017). If this is granted, then all the above four clinical trials are consistent in showing no benefits of therapeutic lung surfactants in ARDS mortality for adult patients. More and improved clinical studies are needed to unambiguously validate, or

invalidate, the efficacy of therapeutic lung surfactants in adult ARDS patients.

Unfortunately, these unsuccessful previous attempts have created a false conception (we believe) in the community that NRDS surfactant therapeutics are fundamentally ineffective in treating adult ARDS. However, the positive results of improved oxygenation levels and reduced mortality rates following SRT in infant and pediatric ARDS patients strongly suggest that improved designs for clinical trials may result in demonstration of its clinical benefits for adult ARDS patients. Understanding the exact reasons behind the findings of these previous clinical studies, particularly the unsuccessful outcomes of SRT in adult ARDS patients, will provide valuable information toward improving in future studies (Grotberg et al., 2017). It is important to note that when NRDS lung surfactant therapeutics were developed, there were also multiple step backs (Notter, 2000). Continued research to develop successful lung surfactants for adult ARDS should not be discouraged. The societal impact of such development would be huge.

6. Lessons from past studies provide directions for future research toward developing new therapeutic lung surfactants targeting adult ARDS

The four large-scale clinical trials involving adult ARDS patients provide three valuable insights. First, not all ARDS patients are suitable for SRT. ARDS patients with direct lung injury are more relevant to SRT than those having indirect causes. Thus, ARDS patients with direct lung injury should be the priority population for future clinical testing, and if this study showed promise, then a follow up study should be considered to explore efficacy in ARDS patients with non-direct lung injury. Second, for the purpose of treating ARDS, therapeutic lung surfactant should be redesigned. As far as NRDS is concerned, animal-extracted lung surfactants are effective because the problem being addressed is lung surfactant deficiency. However, to treat ARDS, a completely different biophysical disease mechanism has to be dealt with, that is, the deactivation of lung surfactants. In ARDS lungs, similarly to what happens to endogenous lung surfactants, instilled therapeutic lung surfactants also become deactivated due to the permeabilization of lung blood vessels, which renders SRT ineffective. Ideal ARDS lung surfactant therapeutics should be designed such that they are resistant to surface inactivation by such compounds as fibrinogen, haemoglobin and albumin, and also to degradation by phospholipases. Lastly, dose parameters should be better optimized for treatment of adult patients. It has been commonly assumed that NRDS treatment parameters should simply be scaled based on lung volume for treatment of adult ARDS patients. Further in-depth studies are required to identify optimal parameters for formulation (surfactant type and concentration) and administration (surfactant dose, liquid volume, etc.).

Aerosol delivery would be ideal in terms of ensuring uniform distribution of lung surfactants and also in terms of avoiding possible complications associated with repositioning patients from side to side during bolus instillation of lung surfactants, particularly in a patient population with homogeneous lung injury. As mentioned earlier, the greatest advantage of aerosol delivery is that an aerosol could be delivered with a CPAP mask or in other situations that do not involve mechanical ventilation. However, aerosol delivery has its limitations. Firstly, aerosol delivery provides surfactant only to areas of the lung that receive airflow; (Porra et al., 2018; Raghavendran et al., 2011; Sinclair et al., 2010) in a heterogeneous lung injury, the areas of the lung that receive the airflow are the alveoli with a functional surfactant system (Porra et al., 2018; Raghavendran et al., 2011; Sinclair et al., 2010). Thus a clinical hurdle of aerosol surfactant delivery is that it may not deliver surfactant to the area of the lung that requires the material. In general, it is likely that aerosol surfactant will be most useful for mild (homogenous) lung injuries or as a maintenance dose following a bolus instillation. The second issue, related to the topic of this review, is the financial aspect. Aerosol delivery of drugs is, in general, mostly suitable for inexpensive medications. The relative amount of surfactant that will actually be deposited in the lung after aerosolization is, likely, in the 5–15% range (Anzueto et al., 1996). Thus, to provide a clinically effective dose, much more material is required than through bolus instillation, which may have financial implications. A cheaper lung surfactant product would be beneficial in this regard. These aspects require careful considerations. Although, on a per-treatment basis, aerosol surfactant therapy would not likely be cheaper than fluid bolus therapy, aerosolized surfactant has the potential to significantly reduce the overall cost of care because of other factors involved, both short- and long-term, such as non-reliance on ventilation for delivery, reduced hospitalization, reduced risk of chronic lung injury, etc. Overall, therefore, there does seem to exist a financial driving force for implementing aerosol delivery.

7. Synthetic lung surfactant is advantageous over animal-extracted lung surfactant in treating ARDS

For use in ARDS treatment, animal-derived lung surfactants are actually not desirable. All animal-derived lung surfactants function by the same “desorption-readsorption” mechanism. Also, regardless of animal source, animal-derived lung surfactants are deactivated by surface deactivating agents (e.g., fibrinogen, haemoglobin, albumin, etc.) by an identical mechanism; the serum proteins (deactivating agents), being more surface active, replace lung surfactants (phospholipids) at the air-water interface (Notter, 2000). If an excess amount of phospholipids are supplied, surface deactivating agents at the air-water interface can be replaced back by phospholipids, which is a very cost-ineffective process. Nevertheless, this has been the underlying concept behind all previous clinical tests. Interestingly, there has been studies that suggests Surfactant Protein A (SP-A) suppresses the inhibitory effects of serum proteins on lung surfactants (Khubchandani and Snyder, 2001). These findings encourage that alternative strategies of boosting endogenous surfactant or limiting turnover should be considered. Further, a possible completely new direction in this field would be to explore new synthetic compounds that have higher surface activity than deactivating agents, e.g., a compound that forms an insoluble monolayer at the air-water interface; such material will not be deactivated even in the presence of serum proteins. Identifying such compound requires exploration beyond phospholipid chemistries.

Lung surfactant formulations based on non-animal-derived synthetic lipids, proteins or peptides have been tested for treating ARDS

Table 3
Synthetic lung surfactants developed or under development.

Product name	Manufacturer	Active ingredient	Current status
ALEC	Britannia Pharmaceuticals	Synthetic DPPC, and egg PG mixed in 7:3 M ratio	Discontinued
Exosurf	Glaxo-Wellcome	Synthetic DPPC, hexadecanol, and tyloxapol in 1:0.111:0.075 weight ratio	Discontinued
Surfaxin (KL4 Surfactant)	Discovery Laboratories	Synthetic DPPC, POPG, palmitic acid, and KL4 in 3:1:0.6:0.12 weight ratio	Transitioned to Aerosurf
Venticute (rSP-C Surfactant)	Altana Pharma	Synthetic DPPC, POPG, palmitic acid, rSP-C, and $CaCl_2$ in 0.634:0.278:0.045:0.018:0.025 weight ratio	Not Marketed
CHF5633	Chiesi Farmaceutici	Synthetic DPPC, POPG, SP-B mimic, SP-C mimic (Seehase et al., 2012)	Under Clinical Trials

and NRDS. However, to date there is none that has been marketed for these indications. Notable synthetic lung surfactant products are tabulated in Table 3. ALEC and Exosurf were the two first synthetic surfactants developed to treat NRDS. These two products saved the lives of premature infants until a more effective animal-extracted lung surfactant, Survanta, was introduced to the market. In a side-by-side comparison between Exosurf and Survanta (N = 1296) in infants having body weights ranging from 501 to 750 g (N = 305), the mortality rate was 44% for Exosurf, and 37% for Survanta; in infants with body weights between 751 and 1000 g (N = 412), the mortality rates were identical at 14% between Exosurf and Survanta; in infants with body weights between 1001 and 1500 g (N = 564), the mortality rate was 5% for Exosurf, and 2% for Survanta (Multicenter, 1996). The reason for the lower efficacy of Exosurf than Survanta is the absence of SP-B and SP-C proteins in Exosurf. All next generation synthetic surfactants (Surfaxin, Venticute, and CHF5633) that are currently under development contain recombinant SP-B/SP-C compounds or their protein/peptide mimics.

Venticute has an interesting history. Venticute is a recombinant SP-C-based lung surfactant which has never tested in NRDS patients. It was developed for ARDS treatment because ARDS has a greater market potential and requires synthetic production of lung surfactants. The latter is because of the large volumetric demand for lung surfactants needed to treat ARDS cases if lung surfactant becomes the standard of care treatment for ARDS. To treat an NRDS infant, 1–4 vials of lung surfactant are needed. To treat an adult ARDS patient (having a much larger lung volume), a proportionately larger amount of surfactant should be used. Assuming a typical value for the dose level of 100 mg/kg, an NRDS patient with 1 kg body weight requires 100 mg of therapeutic lung surfactant. This means (based on simple body weight scaling) that for an adult ARDS patient with 75 kg body weight, 7500 mg of lung surfactant (about 35 vials) would be needed per dose/treatment. The US prevalence for ARDS is estimated to be 190,000 patients per year using the lower bound of the annual ARDS incidence range (56–82 per 100,000 people) (Hudson et al., 1995; Nathens et al., 2004; Angus et al., 2001; Rainer et al., 1999). Considering only ARDS patients with direct lung injury (~50% based past ARDS clinical trial results), about 95,000 ARDS patients would qualify for SRT treatment. Assuming that, on average, 2 doses are given to each patient, the amount of lung surfactant needed annually for treatment of ARDS would be 6.7 million vials (1425 kg of active ingredient). This amount is about 58 times higher than that needed for NRDS treatment (115,000 vials).

Animal lungs from which therapeutic lung surfactants are extracted are obtained from slaughterhouses. USDA estimated that a total of about 28.8 million cattle were slaughtered in the US in 2015 (National Agricultural Statistics Service (NASS), 2016). Typically, about 100 mg of lung surfactant (phospholipids) is produced from one adult cow, and about 1 g of lung surfactant from a calf (NSF I-Corps Interviews, 2017). Since the calf supply is relatively low, by considering only adult cows as the main source of lung surfactant, annually 14.25 million cows (49% of all cows slaughtered in the US each year) would have to be used to meet the demand in the ARDS market. From a production standpoint, this is not a sustainable condition. Further, such external factors as epidemic disease (e.g., mad cow disease) may easily hamper animal-based production of therapeutic lung surfactants without forewarning, which additionally increases risks of supply-demand imbalances.

Taken together, the likelihood of surfactant deactivation and the infeasible supply scenario pose substantial barriers to the use of animal-derived lung surfactants in ARDS treatment. For ARDS applications, alternative therapeutics (lung surfactants of fully synthetic origin that are inert to deactivation by serum proteins and are not constrained by feedstock availability) must be developed. Unlike NRDS, the ARDS market size provide sufficient motivation to invest in developing a new drug for ARDS treatment. Under the simplistic assumption that an ARDS lung surfactant would be priced at the same level as current NRDS therapeutics (~$600 per vial), the US ARDS market is estimated to be $4 billion. This market size is sufficient to justify the investment in developing a new drug product. The ARDS market size will significantly increase further from projected $4 billion, for instance, if lung surfactants can be aerosol-delivered, if lung surfactants exhibit efficacy in early-stage intervention (i.e., in suppressing the inflammatory cascade), or if they produce therapeutic benefits for ARDS patients with indirect lung injury.

8. The future of therapeutic lung surfactant

Over the years the interest in furthering the SRT technology has steadily dwindled. NRDS is now considered a fully treatable disease thanks to advancements in combined use of ventilation/CPAP, steroid (betamethasone) treatment and SRT techniques. The focus in neonatology has been shifted toward such areas as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventicular hemorrhage (IVH), and necrotizing enterocolitis (NEC) (NSF I-Corps Interviews, 2017). The continued unsuccessful outcomes of clinical studies in adult ARDS patients and also of efforts in developing aerosolized formulations have also contributed to this trend. However, recent advancements in aerosolization technology (e.g., vibrating-mesh nebulization) and recombinant protein/peptide synthesis (NSF I-Corps Interviews, 2017; Glaser et al., 2017; Sweet et al., 2017) makes us hope for a leap in improvement in SRT. Considering the significant business development opportunity and potential societal benefits, investments in developing new fully synthetic surfactant therapeutics for ARDS treatment are fully justified. Synthetic lung surfactant may also create opportunities for making SRT more accessible (more affordable) to NRDS patients in less developed countries.

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