Review

nature publishing group

# Evolution of surfactant therapy for respiratory distress syndrome: past, present, and future

Smeeta Sardesai[1], Manoj Biniwale[1], Fiona Wertheimer[1], Arlene Garingo[1] and Rangasamy Ramanathan[1]

Respiratory distress syndrome (RDS) due to surfactant deficiency is the most common cause of respiratory failure in preterm infants. Tremendous progress has been made since the original description that surfactant deficiency is the major cause of RDS. Surfactant therapy has been extensively studied in preterm infants and has been shown to significantly decrease air leaks and neonatal and infant mortality. Synthetic and animal-derived surfactants from bovine as well as porcine origin have been evaluated in randomized controlled trials. Animal-derived surfactants generally result in faster weaning of respiratory support, shorter duration of invasive ventilation, and decreased mortality when compared to first- or second-generation of synthetic surfactants, but some of the second-generation synthetic surfactants are at least not inferior to the animal-derived surfactants. Using a higher initial dose of porcine derived surfactant may provide better outcomes when compared with using lower doses of bovine surfactants, likely, due to compositional difference and/or the dose. Third-generation synthetic surfactant containing peptide analogs of surfactant protein B and C are currently being studied. Less invasive intra-tracheal surfactant administration techniques in spontaneously breathing neonate receiving noninvasive ventilator support are also being evaluated. In the present era, prophylactic surfactant is not recommended as it may increase the risk of lung injury or death. In the future, surfactants may be used as vector to deliver steroids, or used in combination with molecules, such as, recombinant Club Cell Protein-10 (rhCC-10) to improve pulmonary outcomes. Also, noninvasive surfactant administration techniques, such as aerosolization or atomization of surfactant may play a greater role in the future.

Respiratory distress syndrome (RDS) is the leading cause of respiratory insufficiency, as well as mortality and morbidity in preterm infants. The incidence of RDS increases with decreasing gestational age. Sixty per cent of infants born at <28 wk gestation will develop RDS, with incidence of 30% in infants born between 28 and 34 wk gestation, and in less than 5% of infants born after 34 wk (1). In late 1920s, Kurt von Neergaard, a German-born physiologist working in Switzerland identified the function of the pulmonary surfactant in increasing the compliance of the lungs by reducing surface tension (2). In the 1950s, Richard Pattle while working with nerve gases in England speculated that "absence of the lining substance may sometimes be one of the difficulties with which a premature baby has to content" (3). Around the same period, John Clements using a modified Wilhelmy balance working at the US Army Chemical Center in Edgewood, Maryland came to a similar conclusion (4). In 1959, Mary Ellen Avery working with Jere Mead published a seminal article demonstrating that RDS was due to lack of surfactant (5). It is now well established that prematurely born infants with RDS have a developmental deficiency of a surface tension-lowering substance, called, surfactant, in which all of the components that directly contribute to lowering surface tension are reduced or absent (6–8). Genetic and acquired disorders associated with the surfactant system can cause both acute and chronic lung disease. Mutations in the genes encoding the surfactant proteins B and C (SP-B and SP-C) and the phospholipid transporter, ABCA3, are associated with respiratory distress and interstitial lung disease (9). Although heterozygous ABCA3 mutation carriers are mostly asymptomatic, there is growing evidence that monoallelic mutations may affect surfactant homeostasis. Surfactant protein C mutations are dominant or sporadic disorders leading to a broad spectrum of manifestations from neonatal respiratory distress syndrome to adult pulmonary fibrosis.

Pulmonary surfactant is synthesized and secreted by type II pneumocytes, lining the alveoli. Transcription factors and steroids may regulate surfactant synthesis. Human surfactant is a complex mixture primarily composed of dipalmitoyl phosphatidyl-choline (DPPC) and SP-A, SP-B, SP-C, and SP-D. DPPC is the largest fraction (41%) in weight, but surfactant also includes unsaturated phosphatidyl-choline (PC) (25%), phosphatidyl-glycerol (PG) (9%), other phospholipids, cholesterol and other neutral lipids (10). The specific composition plays a major role in the thermodynamic properties of the mixture, melting temperatures being widely different between components. The individual components and their concentrations are highly relevant in the synthetic surfactant design. For example, without hydrophobic SPs,

[1]Department of Pediatrics, Division of Neonatal Medicine, LAC+USC Medical Center and Children's Hospital Los Angeles, Keck School of Medicine of the University of Southern California, Los Angeles, California. Correspondence: Rangasamy Ramanathan (ramanath@usc.edu)

Received 13 May 2016; accepted 30 September 2016; advance online publication 9 November 2016. doi:10.1038/pr.2016.203

DPPC's adsorption kinetics is very slow. The fast adsorption velocity is crucial to maintain the integrity of the air-liquid interphase of the lungs. Among the four SPs, two hydrophobic proteins, SP-B and SP-C, play crucial roles in the adsorption and spreading of the DPPC and help to maintain stability in the lung. SP-A and SP-D are lectin proteins and confer innate immunity as they have carbohydrate recognition domains that allow them to coat bacteria and viruses promoting phagocytosis by macrophages, helping to maintain sterility in the lung. Lipids and SP-B and SP-C are co-packaged with lamellar bodies and secreted into the airspace. In the presence of calcium, SP-A interacts with unraveling of lamellar bodies after release from Type II cells by exocytosis to form tubular myelin, a highly organized, large-aggregate surfactant form that comprises most of the active surfactant fraction present in the subphase. Monolayers and multilayers of phospholipids are generated at the air-liquid interface. Formation of this surface film is enhanced by SP-B and SP-C, which maintain stability of the lipid film during the respiratory cycle. By adsorbing to the air-liquid interface of alveoli, with hydrophilic head groups in the water and the hydrophobic tails facing towards the air, the main lipid component of surfactant, DPPC, reduces surface tension. Plasmalogen, an antioxidant phospholipid has also been shown to work synergistically with SP-B to spread the DPPC and further lower surface tension (11). Role of other acidic phospholipids, such as, phosphatidyl-inositol, -glycerol and -ethanolamine, neutral lipids, and cholesterol is largely unknown. Surfactant is catabolized by alveolar macrophages and type II epithelial cells recycle 90% of DPPC. Synthesis, storage and secretion of surfactant take several hours. Surfactants in preterm infants with RDS have a prolonged half-life of about 3 d. Term infants have a surfactant storage pool of approximately 100 mg/kg of surfactant, while preterm infants have an estimated pool size of 4–5 mg/kg at birth (10). Exogenous surfactant therapy acutely increases the pool size and improves pulmonary gas exchange until enough endogenous surfactant is released from the storage pool in preterm infants. Surfactant is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.

The use of exogenous surfactant to prevent and treat RDS has been standard therapy for more than three decades (8). During this period several commercially available surfactants, either synthetic or derived from animal lungs have been shown to be clinically effective (12,13). Many clinical trials have demonstrated that both synthetic surfactants and animal-derived surfactant preparations are effective in the prevention and treatment of RDS.

## TYPE OF SURFACTANT: SYNTHETIC VS. ANIMAL-DERIVED SURFACTANTS

### Past: First-Generation Synthetic Surfactant Trials

Two studies published in the 1960s using nebulized DPPC to treat RDS were largely negative (14,15). This is due to the fact that at physiologic temperatures, DPPC exists as a crystalline gel and rigid, thus, hindering its adsorption at the air-liquid interface. In 1987, a 10-center trial of a synthetic surfactant, pumactant (artificial lung expanding surfactant, ALEC) composed of DPPC, and PG, in very preterm infants was published (16). Babies were randomized to receive approximately 100 mg of pumactant suspension or 1 ml saline. This was given at birth into the pharynx with up to three more endotracheal doses if the baby was intubated during the first day. Significant reduction in mortality and respiratory support were reported. The development of alternate additives to replace the adsorptive roles of SP-B and C, namely, tyloxapol and hexadecanol, led to first FDA-approved protein-free surfactant, colfosceril palmitate (Exosurf, Burroughs Wellcome, London, UK) for treatment of RDS in United States. Several randomized clinical trials using Exosurf for the prevention and treatment of RDS showed decrease in neonatal and infant mortality and in air leaks (12,17). However, a meta-analysis by Soll and Blanco (18) in 2001 showed that treatment with protein-free first-generation synthetic surfactants, such as colfosceril palmitate or pumactant, was associated with increased mortality and a greater risk of pneumothorax when compared to animal-derived surfactants. The inferiority of first-generation synthetic surfactants is attributed to lack of SP-B and SP-C.

### Second-Generation Synthetic Surfactants

Due to theoretical concerns for infectious and antigenic complications from animal derived surfactants, poor response to first-generation synthetic surfactants, and possible concerns for the cost of their production, second-generation synthetic surfactants containing compounds designed to mimic the structure and actions of SP-B or SP-C were developed. The presumed advantages of such surfactant are the consistency in the amounts of these protein mimics and the possibility to reduce the theoretical risks related to animal-to-human transmission of infections. The two surfactants that have been studied in humans are lusupultide (Venticute, Takeda Pharmaceuticals, Zurich, Switzerland) and lucinactant (Surfaxin; Discovery Laboratories, Warrington, PA). Lusupultide contains recombinant SP-C. It has not been studied in neonates and has only undergone trials in adults with acute lung injury in which short-term physiologic benefits were not accompanied by improvements in survival (19). Lucinactant contains two phospholipids, a fatty acid, and sinapultide (KL4), a 21-amino acid hydrophobic synthetic peptide, designed to have similar activity to SP-B. Sinapultide is considered to be more resistant to inactivation by endogenous serum proteins and reactive oxygen species than naturally occurring SP-B (20,21). The US Food and Drug Administration approved lucinactant in 2012. The commercial preparation of Lucinactant was available as a gel formulation in single-use vials of 8.5 ml. Prior to use, it requires warming for 15 min in a dry block heater preheated to 44 °C. The vial is then shaken vigorously until it becomes a free-flowing suspension and is allowed to cool to body temperature. The approved dose was 5.8 ml/kg given intratracheally as frequently as every 6 h for up to four doses in the first 48 h of life (22).

## COMPARISON OF FIRST-GENERATION SYNTHETIC AND ANIMAL-DERIVED SURFACTANTS WITH SECOND-GENERATION SYNTHETIC SURFACTANT

Lucinactant was compared to colfosceril palmitate and beractant by Moya *et al.* (23). They enrolled 1,294 infants who were ≤32 wk gestation and 74% were exposed to antenatal steroids. Surfactant was administered prophylactically within the first 30 min of life. There was a significant reduction in RDS at 24 h after birth as well as a significant reduction in RDS-related mortality in the lucinactant group. Lucinactant also decreased BPD rates at 36 wk compared to colfosceril palmitate. There was a significant reduction of RDS-related deaths in the lucinactant group compared to beractant, and overall mortality was also marginally higher with beractant. However, no differences in other morbidities of prematurity were identified between the lucinactant and beractant groups. The Surfaxin Therapy Against RDS (STAR) study by Sinha *et al.* (24) compared lucinactant with poractant alfa among infants with gestational ages ranging from 24 to 28 wk and birth weights 600–1,250 g as a noninferiority trial. The dose of poractant alfa (175 mg/kg or 2.2 ml/kg/dose) was equivalent to that of lucinactant (175 mg/kg or 5.8 ml/kg), although slightly less than the dose recommended by the manufacturer (200 mg/kg). The study was stopped with about half of the patients enrolled due to slow recruitment. In these two published randomized trials (23,24), lucinactant has been shown to be safe and effective and to reduce mortality associated with RDS. These data suggest that this second-generation synthetic surfactant is at least comparable with animal-derived preparations in outcomes, and superior to first-generation synthetic surfactant. One of the difficulties with the use of lucinactant is its high viscosity at room temperature, the need for warming prior to use, and the large volume. Lucinactant was withdrawn from the market in 2015. Currently, neither the first- nor the second-generation synthetic surfactants are available for intratracheal administration to treat RDS in the United States or elsewhere.

### Present: Preclinical Studies With Animal-Derived Surfactants

In 1972, Enhorning and Robertson showed that preterm rabbits treated with natural surfactant containing both phospholipids and proteins could ameliorate the signs of RDS (25). In 1973, they showed that pharyngeal deposition of natural surfactant was effective (26). Adams *et al.* (27) also demonstrated beneficial effects of tracheal instillation of natural bovine surfactant in lambs in 1978.

## CLINICAL TRIALS WITH ANIMAL-DERIVED SURFACTANTS

Fujiwara *et al.* reported the first successful exogenous surfactant administration in newborn infants with RDS in 1980 in 10 preterm infants, with a surfactant preparation from minced bovine lungs (Surfactant TA) (28). After this report, several randomized, controlled, clinical trials have been performed using bovine or porcine surfactants. Many different animal derived surfactants are available worldwide. Three major animal-derived surfactants studied have unique features, e.g., lavage vs. solvent extraction for calf lung surfactant extract (Infasurf, Forest Labs, New York, NY) and specific additives in the lipid extract of bovine mince, beractant (Survanta, Abbott Laboratories, Columbus, OH). These unique features manifest in the performance of the surfactants as seen in the comparative studies. Poractant alfa (Curosurf, Chiesi Farmaceutici, Parma, Italy), a porcine surfactant developed by Bengt Robertson and Tore Curstedt was used in a pilot clinical trial in 1987 (29). This surfactant is unique in that, apart from being produced from pig lungs, it undergoes an additional step, called, liquid gel chromatography, leaving only polar lipids and high amounts of SP-B and plasmalogen with a phospholipid concentration of 80 mg per ml (**Table 1**). Furthermore, poractant alfa, with the highest concentration of phospholipids, SP-B and plasmalogen compared to beractant and calfactant has the lowest volume of administration of any currently available surfactants.

## STUDIES COMPARING BOVINE-DERIVED SURFACTANTS

Trials comparing beractant and calfactant demonstrated no differences in clinical outcomes or dosing complications. However, among infants treated for established RDS, a subgroup of those who received calfactant had a significantly longer interval between doses, a lower inspired oxygen concentration, and a lower mean airway pressure in the first 48 h of life than infants treated with beractant (30). Bloom and colleagues (31) compared calfactant to beractant in infants ≤ 29 wk and with birth weight <1,250 g. Early prophylactic use of calfactant compared to beractant showed benefits over the rescue treatment strategy. Prophylactic calfactant treatment resulted in decreased duration of mechanical ventilation (20 ± 22 vs. 27 ± 26 d, mean ± SD, $P = 0.01$) and decreased duration of supplemental oxygen (36 ± 39 vs. 46 ± 48 d, mean ±

**Table 1.** Composition of most commonly used animal-derived surfactants

| Surfactant | Preparation | Phospholipids (mg/ml) | DSPC (mg/ml) | Total proteins (mg/ml) | SP-B (mg/ml) | SP-B (mg per mm PL) | SP-C (mg per mm PL) | PLMGN (mol% total PL) |
|---|---|---|---|---|---|---|---|---|
| Poractant alfa (Curosurf) | Minced porcine lung extract—purified via liquid gel chromatography | 76 | 30 | 1 | 0.45 | 2–3.7 | 5–11.6 | 3.8 ± 0.1 |
| Beractant (Survanta) | Minced bovine lung extract/ DPPC, palmitic acid, tripalmitin | 25 | 11–15.5 | <1 | Not specified | 0–1.3 | 1–20 | 1.5 ± 0.2 |
| Calfactant (Infasurf) | Bovine lung lavage/ DPPC, cholesterol | 35 | 16 | 0.7 | 0.26 | 5.4 | 8.1 | Not specified |

DSPC, disaturated phosphatidylcholine; PLMGN, plasmalogen; SP, surfactant protein.

SD, $P = 0.02$). Frequency of air leaks, pulmonary hemorrhage, severe grade 3 or 4 intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and sepsis were similar between the groups. The mortality rate, however, was slightly higher in the calfactant treated infants compared to the beractant treated infants (14 vs. 8%, $P = 0.06$). For infants <600 g, mortality was 63% in infants treated with calfactant vs. 26% in infants treated with prophylactic beractant ($P = 0.007$). Another study by Bloom and Clark (32) of premature infants less than 30 wk showed no difference between patients treated with calfactant compared to beractant for any outcomes in either the rescue treatment or the prophylaxis protocols. No differences in the need for two or more doses were reported between these two surfactants in any of these trials. However, both these trials (31,32) were stopped early due to slow recruitment and therefore, the authors could not accept or reject the null hypothesis of no difference.

In a retrospective study comparing calfactant ($n = 1,115$) vs. beractant ($n = 4,054$) by Clark *et al.* (33), there was no difference in weight-specific mortality or morbidity. In infants <601 g, the mortality rates were similar (44 vs. 43%, respectively; $P = 0.94$). Study interpretation was complicated by a slightly higher percentage of inborn infants in the calfactant than beractant group (89 vs. 85%; $P = 0.01$). No differences in clinical outcomes were observed in comparative trials between bovine lung lavage surfactant and modified bovine minced lung surfactant (34).

## STUDIES COMPARING BOVINE VS. PORCINE SURFACTANTS

The first multicenter trial of poractant alfa published in 1988 showed reduced pulmonary air leaks and neonatal mortality in preterm infants with severe RDS (35). A second trial, by Speer *et al.* (36) demonstrated that multiple doses of poractant alfa were more effective than a single dose. Subsequent trials of poractant alfa showed that early treatment was more effective than later administration (37–39). Six randomized clinical trials comparing poractant alfa and beractant have been published (40–45). In all these trials, treatment with poractant alfa resulted in faster weaning of oxygen and mean airway pressure, less need for two or more doses, less days on mechanical ventilation, lower mortality in ≤32 wk gestation infants, less air leaks and patent ductus arteriosus (PDA), and higher rates of survival without BPD when compared to beractant treated infants. In a systematic review and meta-analysis by Singh *et al.* (46) of five randomized controlled trials involving 529 infants compared poractant alfa vs. beractant for rescue treatment. None of the trials studied surfactant prophylaxis, and none compared poractant alfa with calfactant. The incidence of oxygen dependence at a postmenstrual age of 36 wk was similar for poractant alfa and beractant. Infants treated with poractant alfa at 100 mg/kg (low dose) or 200 mg/kg (high dose) exhibited statistically significant reductions in deaths (relative risk: 0.51 (95% confidence interval: 0.30–0.89)), the need for redosing (relative risk: 0.71 (95% confidence interval: 0.57–0.88)), oxygen requirements, duration of oxygen treatment, and duration of mechanical ventilation. The test of heterogeneity yielded positive results for the latter two outcomes. The difference remained statistically significant for deaths and the need for redosing with high-dose poractant alfa but not for low-dose poractant alfa. Another meta-analysis by Fox and Sothinathan (47) concluded that results of randomized, controlled trials of different preparations of animal derived surfactants suggest that poractant alfa reduces the need for repeat dosing, associated with fewer complications of administration, leads to better short-term oxygenation and may reduce the risk of mortality compared to beractant. Similar results were also reported in the meta-analysis by Halliday (48). In the most recent Cochrane Reviews published in 2015, significant differences in clinical outcome were noted in the comparison trials of beractant compared with poractant alfa including a significant increase in the risk of mortality prior to discharge, death, or oxygen requirement at 36 wk postmenstrual age, PDA requiring treatment and patients receiving >1 dose of surfactant in infants treated with beractant compared with poractant alfa (34). The difference in these outcomes was limited to studies using a higher initial dose of poractant alfa. Although these studies suggest that the differences observed between poractant and beractant are related to the higher phospholipid dosage of the former, one cannot exclude that other factors such as animal source (porcine vs. bovine) or chemical composition contributing to those findings. Current literature lack dose-equivalent comparison groups with appropriate sample size.

In a large retrospective study, Ramanathan *et al.* compared 14,173 infants treated with poractant alfa, calfactant or beractant and reported significantly higher mortality rates in infants treated with calfactant or beractant when compared to poractant alfa treated infants (49). Overall mortality tended to be lower in infants treated with poractant alfa (3.61%) compared to beractant (4.58%, $P = 0.053$) or calfactant (5.95%, $P = 0.043$). In infants with birth weights 500–749 g, a significantly lower mortality rate was observed for those treated with poractant alfa (11.72%) when compared with those treated with calfactant (20.67%, $P < 0.001$), and/or beractant (17.39%, $P < 0.011$). A third retrospective study evaluating comparative effectiveness between these three surfactants in 51,282 infants showed no differences in mortality (50). However, more than 50% of the infants in this study were >31 wk and late preterm infants. In addition, the authors did not account for all known confounders.

## FUTURE: THIRD-GENERATION SYNTHETIC SURFACTANTS

Third-generation synthetic surfactant containing DPPC, 1-palmitoyl-2-oleoyl-PG (POPG) and SP-B and SP-C analogs has been shown to be superior, when compared to calfactant in an animal model of acute RDS and is better equipped to handle surfactant inactivation in chemical acute lung injury than a synthetic surfactant with only a single surfactant peptide or animal-derived surfactant (51). For the first time in an *in-vivo* model, a synthetic surfactant containing both SP-B and SP-C analogues (CHF 5633) resisted inactivation better than poractant alfa in preterm lambs (52). A first phase-I human trial on synthetic surfactant CHF 5633 in RDS has been completed in

Germany and UK centers (ClinicalTrials.gov NCT01651637) and the results are pending (53). A phase-II multicenter double-blinded clinical trial (54) comparing CHF 5633 with poractant alfa for RDS treatment is currently ongoing in the United States (ClinicalTrials.gov NCT02452476).

## TIMING OF SURFACTANT TREATMENT: PROPHYLACTIC VS. EARLY, DELAYED RESCUE, OR LATE RX

### Past

Studies in the early 1990s when antenatal corticosteroid use was less than 50% showed that prophylactic surfactant given within 15 min of birth in a fluid filled lung allowing better distribution of surfactant was associated with better outcomes than rescue therapy. However, with increasing use of antenatal corticosteroids and routine use of continuous positive airway pressure (CPAP) during delivery room stabilization, prophylactic surfactant therapy is associated with more risk of death or BPD (relative risk 1.13, 95% CI: 1.02, 1.25) (55). In a population with a high usage of antenatal steroids and routine use of NCPAP in the delivery room, prophylactic surfactant therapy is no longer recommended.

### Present: Early vs. Delayed Rescue, and Late Surfactant Therapy

In 1999, Verder *et al.* in a trial comparing early vs. late selective surfactant administration in preterm infants on nasal CPAP (NCPAP), randomized for intratracheal surfactant treatment when reaching lower vs. higher oxygen requirement (FiO2 0.37–0.55 vs. 0.56–0.77 for >30 min), showed that early rescue treatment resulted in significantly less need for intubation and/or death before 7 d of age or before discharge from the hospital (56). Ten years later, in 2009, a similar trial published from Colombia, South America demonstrated significantly less need for intubation and less air leaks with early rescue treatment (57). Reduction in the need for mechanical ventilation is an important outcome when medical resources are limited and may result in less BPD in both developed and low resource areas. Late surfactant treatment beyond the first week of life was recently evaluated in two RCTs (58,59). Ballard RA *et al.* (58) found no difference in BPD at 36 or at 40 wk corrected gestational age, however, in the study by Hascoet JM *et al.* (59) reduced respiratory morbidity prior to 1 y of age was reported, raising the possibility for long-term benefits of late surfactant therapy.

### Future

Exact timing for administering surfactant is still under debate, especially in infants receiving noninvasive ventilation (NIV). Supplemental oxygen needs may be different based on the pressures used during NIV. Studies evaluating the timing based on oxygen requirement while on NIV are being evaluated. Future research should focus on optimizing timing for individual patients with not only oxygen requirement but also taking into the consideration of pressures, gas exchange, clinical condition and radiologic findings.

## TECHNIQUES OR SURFACTANT ADMINISTRATION

### Past

In the past, surfactant was given to preterm infants who were on mechanical ventilation due to respiratory failure from RDS. This method resulted in prolonged mechanical ventilation (MV) and no decrease in BPD. Adverse pulmonary and nonpulmonary outcomes directly correlated with the duration of invasive mechanical ventilation.

### Present

At present, intubation, surfactant and extubation (INSURE) technique first described more than 24 y ago by Verder *et al.* is increasingly being used (60). INSURE procedure involves intubation and surfactant administration using an endotracheal tube and extubation after a brief period of mechanical ventilation. Often, premedication with opioids are used during this procedure. Failure or reluctance to extubate following surfactant administration is common even with reversal of sedation using opioid antagonists. In premature infants with

**Table 2.** Techniques of modified INSURE in spontaneously breathing preterm infants without using an endotracheal tube

| Method | Tube/catheter | Dose and mode of surfactant delivery | Premedication/sedation |
|---|---|---|---|
| Cologne method | 4 or 5-Fr. feeding tube | 100 mg/kg, given over 1–3 min | Atropine, sedation and analgesia (optional) |
| SWI | 4 Fr. Feeding tube | 100 mg/kg given over 1-5 min | Atropine (optional) |
| Hobart method | 16 G Angiocath | 100–200 mg/kg, given over 15–30 s | Sucrose |
| AMV/NINSAPP method | Catheter using Magill forceps | 100 mg/kg, given over 1–3 min | Atropine, sedation and nalgesis-(optional) |
| LISA | 1.3 mm diameter feeding tube using Magill forceps | 200 mg/kg, given over 2–5 min | None |
| Take Care | 5 Fr. Feeding tube | 100 mg/kg, given over 30–60 s | None |
| SONSURE | 4 Fr. Feeding tube | 100 mg/kg, given over 1–3 min | Atropine |
| Karolinska method | 5 Fr. × 30 cm catheter | Given over 30 s | Atropine, fentanyl |
| ECALMIST study | 17 G vascular catheter, 133 mm long, | 5 ml/kg, 0.25–0.5 ml bolus over 20–30 s | None |
| SAINT trial | 300 mm long catheter | Not specified | Narcotic analgesia |
| MiSurf trial | Feeding tube | 4 ml/kg | Not specified |

**Table 3.** Surfactant therapy: type, timing, and techniques

| | Past | Present | Future |
|---|---|---|---|
| Type of surfactant | Synthetic: Colfosceril palmitate (exosurf); Pumactant (ALEC); Turfsurf (Belfast Surfactant); Lusupultide (Venticute); Lucinactant (Surfaxin); human amniotic fluid surfactant | Animal derived surfactants: Surfactant-TA, Japan; Poractant alfa (Curosurf); cuban natural exogenous surfactant (Surfacen); Beractant (Survanta); Calfactant (Infasurf); BLES; SF-RI 1 bovine surfactant (Alveofact); Semisynthetic surfactants: (Newfactan, Korea) | Third-generation synthetic surfactant with SP-B and SP-C mimics - CHF-5633 |
| Timing of surfactant Rx | Prophylaxis | Early, rescue | Early, targeted |
| Technique | Surfactant in mechanically ventilated patients | INSURE; mINSURE; Via LMA in babies >1,000 g | mINSURE; Aerosolization; Nebulization; Atomization; Via LMA |

BLES, Bovine Lipid Extract Surfactant; LMA, laryngeal mask airway.

RDS, strategies to avoid intubation and invasive positive pressure and mechanical ventilation are being sought. Tracheal intubation may damage the larynx or trachea and requires the use of sedatives and pain medications that have undesirable side effects. Also, positive pressure and mechanical ventilation can damage the preterm lung and its avoidance may decrease the incidence of chronic lung disease (CLD). Leone *et al.* (61) showed that INSURE technique resulted in more sustained oxygenation compared to rescue surfactant administration during invasive mechanical ventilation. In addition, premature infants treated with INSURE developed low respiratory comorbidities, including pneumothorax, BPD, and BPD or death ($P = 0.04$). A recent meta-analysis (62) included nine trials (1,551 infants) and compared INSURE with NCPAP alone. There were no statistically significant differences between early INSURE and NCPAP alone for all outcomes assessed (combined outcome of BPD and/or death, BPD, death, air leaks, severe IVH, neurodevelopmental delay, or death and/or neurodevelopmental impairment). Authors concluded that, "currently, no evidence suggests that either early INSURE or NCPAP alone is superior to the other. There is concern that even a brief period of ventilation can induce lung injury in the vulnerable preterm population. Furthermore, surfactant distribution may be suboptimal when surfactant is given using positive pressure ventilation. Surfactant administration via laryngeal mask airway (LMA) has been described in several small studies demonstrating safety and feasibility in larger preterm infants (63). In a randomized trial of LMA vs. INSURE, Pinheiro *et al.* showed decreased need for mechanical ventilation in the LMA group in preterm infants >29 wk and birth weight >1,000 g. This technique is a very good option in low-income countries with limited resources to administer surfactant, especially, in moderately preterm infants with RDS (64).

Another technique, known as, modified INSURE (mINSURE) or less invasive surfactant administration (LISA) is currently being studied in many centers around the world. This technique involves surfactant administration using a feeding tube, umbilical catheter, or a small angiocatheter while the patient is breathing spontaneously and receiving noninvasive respiratory support. Several alternate names are used to describe mINSURE procedure (65) (**Table 2**). For example, minimally invasive surfactant (MIST), avoidance of mechanical ventilation (AMV), surfactant without intubation (SWI), nonintubated surfactant application (NINSAPP), Take Care method, Sonda Nasogastrica SURfactante Extubacion (SONSURE), Early CPAP and Large volume MIST (ECALMIST), and Minimally Invasive SURF administration (MISURF) are some of terms used to describe mINSURE technique. Take Care technique in preterm infants on CPAP was found to be feasible by Kanmaz *et al.* (66). In this study, they compared LISA using a feeding tube during spontaneous breathing along with NCPAP (Take Care) with the INSURE procedure. Duration of NCPAP and MV were significantly shorter in the Take Care group compared to INSURE group. Since the Take Care technique decreased the need for and duration of MV, that might have impacted the reduction of chronic lung disease rates in the Take Care group (relative risk −0.27, 95% confidence interval −0.1 to −0.72). In a retrospective study by Klebermass-Schrehof *et al.* (67) they assessed LISA technique in a cohort of 23–27 wk gestation infants at a single-center and compared them to historical controls. They found significantly higher survival rates (75.8 vs. 64.1%), less IVH (28.1 vs. 45.9%), severe IVH (13.1 vs. 23.9%), and cystic periventricular leukomalacia (1.2 vs. 5.6%) in the infants treated with LISA method compared to their historical controls of invasive surfactant delivery. In a similar study, Krajewski *et al.* (68) found that surfactant replacement therapy without intubation while receiving NCPAP in preterm infants was associated with significantly lower need for intubation and mechanical ventilation compared to the INSURE method (19.2 vs. 65%). In addition, better pulmonary outcomes were seen with the new method of surfactant replacement. BPD in the study group was significantly lower (15.4%) compared to the INSURE group (40%). In a recent multicenter trial from German neonatal network, NINSAPP technique in preterm infants 23–26 wk gestation resulted in significantly higher survival without major complications (50.5 vs. 35.6%, absolute risk reduction 14.9, 95 CI: 1.4, 28.2, $P = 0.02$) compared to surfactant via endotracheal tube in infants on mechanical ventilation (69). MIST technique using an umbilical catheter inserted 2 cm below the vocal cords also has been shown to result in a rapid and homogenous increase in end-expiratory lung volume and improved oxygenation (70). Further studies are needed to refine instillation techniques, use of sedation or

analgesia, choosing optimal surfactant dose and selection of preterm infants who would benefit most.

### Future

The search for even more "gentler" methods to deliver surfactant for example, via aerosolization, nebulization, or atomization continues. Potential advantages of administering aerosolized surfactant include avoidance of hypoxemia, more homogenous distribution, less need for airway as well as mechanical ventilation, and less volume. Even though the animal studies have demonstrated promising results there have been a limited clinical studies demonstrating efficacy of this route. Finer NN *et al.* published an open-label pilot study of aerosolized lucinactant in preterm neonates on NCPAP to prevent RDS. They concluded that aerosolized surfactant could be safely given via NCPAP (71). Two doses of beractant administered as an aerosol using 100 mg phospholipid/kg or 200 mg phospholipid/kg is being evaluated (NCT02294630).

## COMBINATION THERAPIES

Chronic lung injury is primarily due to persistent inflammation, triggered by infection, mechanical ventilation, and or oxygen. Release off proinflammatory cytokines leads to aberrant repair of the developing lung in preterm infants. Anti-inflammatory therapy in combination with surfactant may help reduce BPD or chronic respiratory morbidity (CRM).

## INTRATRACHEAL INSTILLATION OF BUDESONIDE USING SURFACTANT AS A VEHICLE

Lung inflammation plays a crucial role in the pathogenesis of BPD and glucocorticoid is one potential therapy to prevent BPD. In a pilot study by Yeh *et al.* (72), early intratracheal instillation of budesonide using surfactant as a vehicle in 116 very-low-birth-weight infants with severe radiographic evidence of RDS requiring mechanical ventilation resulted in significantly lower death or BPD compared with infants in the control group who had received surfactant without budesonide (31.7 vs. 60.7%, $P = 0.003$). No clinically significant adverse effects were observed during the study and at the time of the follow-up assessment at 2–3 y of age. Recently, same investigators reported results from a randomized multicenter study of using surfactant with budesonide in 265 very-low-birth-weight infants (73). Death or BPD was 42% in the intervention group compared to control group (66%) with number need to treat to prevent death or BPD of 4.1 (95% CI: 2.8, 7.8, $P \leq 0.001$). More studies are needed using this technique as both these studies had high BPD rates in the control population. In the future, intratracheal instillation of budesonide using surfactant as a vehicle may play a role in the prevention of BPD in extremely-low-birth-weight infants.

## SURFACTANT AND RECOMBINANT CLUB CELL PROTEIN-10 (RHCC-10)

Club Cell protein-10 (CC-10) is one of the most abundant protein produced endogenously by airway epithelial cells and plays a significant role in airway epithelial repair, airway immunomodulation, and inhibits NF-kB pathway in the airways. Preterm infants with RDS/BPD have lower levels of CC-10 in the tracheal aspirate. A phase II trial evaluating intratracheal use of rhCC-10 in surfactant treated preterm infants has been completed and results are pending (NCT 01941745) (74).

In summary, understanding surfactant composition, function, and therapeutic usefulness has increased exponentially over the last 50 y. Exogenous surfactant therapy has become one of the most common procedures performed for the treatment of RDS in preterm infants globally. Composition, timing, and techniques of administering surfactant have been evolving over time (**Table 3**). Prophylactic surfactant therapy may only have a limited role where antenatal corticosteroid administration rates are low. At present, animal-derived surfactants are the standard of care for RDS. Several national guidelines based on local incidence of RDS or local practices have been published (75,76). Future research of surfactant therapy should focus on using surfactant as a vehicle to deliver anti-inflammatory molecules, and less invasive or noninvasive modes of surfactant administration.

### STATEMENT OF FINANCIAL SUPPORT

No funding was secured for this review manuscript.

Disclosure: R.R. has served as a consultant or recipient of research grant support from Burroughs Wellcome, Abbott and Chiesi, USA. R.R. has no stocks in any of the companies and do not accept any honorarium for his international talks. He donates all honorarium received when giving talks on behalf of any company in the USA or outside to charity organizations to help mothers, newborn infants and children around the world. The authors have no financial relationship relevant to this article to disclose.

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