REVIEW ARTICLE

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Use of surfactant beyond respiratory distress syndrome, what is the evidence?

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Surfactant replacement therapy is currently approved by the United States Food and Drug Administration (FDA) for premature infants with respiratory distress syndrome (RDS) caused by surfactant deficiency due to immaturity. There is strong evidence that surfactant decreases mortality and air leak syndromes in premature infants with RDS. However, surfactant is also used "off-label" for respiratory failure beyond classic RDS. This review discusses current evidence for the use of off-label surfactant therapy for (1) term infants with lung disease such as meconium aspiration syndrome (MAS), pneumonia/sepsis, and congenital diaphragmatic hernia (2) premature infants after 72 h for acute respiratory failure, and (3) the use of surfactant lavage. At last, we briefly describe the use of surfactants for drug delivery and the current evidence on evaluating infants for surfactant deficiency.

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INTRODUCTION

In 1959, Avery and Mead discovered that respiratory distress syndrome (RDS) in premature infants is caused by a lack of surfactant [1]. Since then, research has enhanced our understanding of the role of surfactants in respiratory physiology and various neonatal lung disorders. Surfactant is produced by type II alveolar epithelial cells and is composed of ~70 to 80% phospholipids, 10% neutral lipids, and 8% protein that is comprised of four specific surfactant-associated proteins (SP) named SP–A, SP–B, SP–C and SP–D [2]. With its amphiphilic property, surfactant decreases surface tension at the air-fluid interface in alveoli, allowing the alveoli to remain open during the exhalation phase of the respiratory cycle, and facilitates optimal gas exchange. [2] Exogenous surfactant was first successfully used by Fujiwara when he showed significant clinical improvement in ten neonates with severe RDS who received modified natural surfactant that included SP-B and SP-C [3]. Since then, numerous clinical trials have been done to test natural and synthetic surfactants for RDS and other lung disorders in which surfactants may be dysfunctional [4]. By the early 1990s, surfactant administration was well-established as a safe and effective therapy for RDS in premature infants. There is strong evidence that surfactant decreases mortality and air leak syndromes in premature infants with RDS [5–8] Colfosceril, a synthetic surfactant, was the first commercially available surfactant that was approved by the FDA in 1990; however, it is no longer used in the United States. The natural surfactants beractant, calfactant, and poractant alfa were subsequently approved by the FDA in 1991, 1998 and 1999, respectively. It eventually became clear that "natural surfactant," containing the surfactant proteins SP-B and/or SP-C provided greater early improvement in requiring ventilator support, fewer air-leak syndrome, and death compared to synthetic surfactants containing neither of these proteins in infants with RDS [9]. This is primarily because the hydrophobic proteins SP- B and SP -C, improve adsorption properties at the alveolar surface [6].

Currently, the FDA recommends using exogenous surfactants, specifically in preterm infants with RDS in the first 72 hours of age (Table 1). With the high efficacy and safety profile of surfactant in neonates, it has also been used beyond FDA approval [10, 11]. In this review, we will focus on the evidence available for off-label use for 1) term infants with respiratory disease in which surfactant is inactivated (e.g. meconium aspiration syndrome (MAS) or pneumonia); 2) premature infants who may have slower surfactant system maturation/ post-surfactant slump (surfactant inadequacy) leading to hypoxic respiratory failure outside of the original 72 h of age treatment target range; 3) premature infants with evolving or established chronic lung disease, bronchopulmonary dysplasia (BPD), who have an acute but significant respiratory exacerbation, and 4) the use of "surfactant lavage" for respiratory failure. Moreover, there are two additional groups who receive surfactant in NICUs: term infants, especially "early term" infants at 37–38 weeks' (w) gestation who are felt to have surfactant immaturity despite their full-term gestational age (GA) [12]; and very ill NICU infants with acute lung injury/acute respiratory distress syndrome (ARDS) often associated with an acute inflammatory illness such as sepsis or necrotizing enterocolitis (NEC). In a systematic review/meta-analysis by Ramaswamy et al., they described that nearly half of all term and late preterm infants with RDS received surfactant (46%) despite low certainty of evidence in general. In late preterm to early term infants with respiratory failure and known prenatal risk factors for surfactant deficiency such as lack of antenatal steroids, male sex, elective cesarean

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section, multiple gestation, and maternal diabetes [13, 14], use of exogenous surfactant may show clinical improvement. Given that the majority of infants ˃34w gestation have good outcomes, it would be difficult to design a study with sufficient power to show meaningful outcomes in these group of infants. We will focus on those groups with more robust data to support surfactant usage.

SURFACTANT USE IN TERM INFANTS WITH PARENCHYMAL LUNG DISEASE

Surfactant has been used for term and near-term infants with secondary surfactant deficiency/ surfactant inactivation. Auten et al. in 1991 [15] demonstrated improvement in oxygenation in 14-term babies with MAS or "pneumonia" (diagnosis based on radiographic evidence of diffuse coarse infiltrates, pleural fluid, or complete opacification in the absence of evidence suggestive of cardiogenic pulmonary edema; all had negative blood and tracheal aspirate cultures although one had GBS antigen detected in urine) with exogenous surfactant. Since then, several randomized trials and post hoc analyses have confirmed that surfactants in term infants with hypoxic respiratory failure (HRF) can reduce the need for extracorporeal membrane oxygenation (ECMO). Hintz et al. noted that the use of surfactant, along with high-frequency ventilation and nitric oxide (iNO), was one of the major clinical practice changes in the 1990s that was associated with a decrease in the use of ECMO for infants with HRF [16].

Meconium aspiration syndrome

MAS is a complex, severe neonatal respiratory disorder. It is caused by the interplay of several factors that impede gas exchange: chemical injury to the respiratory epithelium from meconium components, inflammation in the lung parenchyma from activation of neutrophils and the complement system, inactivation of surfactant due to meconium and exudate from the alveolar-capillary leak, and obstruction of smaller airways leading to significant atelectasis [17]. Significant hypoxemia can be caused by airway obstruction from meconium, increased reactivity of pulmonary vessels leading to pulmonary vasoconstriction and persistent pulmonary hypertension of the newborn (PPHN), and surfactant inactivation leading to alveolar collapse requiring high-pressure ventilation to keep the alveoli open, causing further injury to the lungs and potentially more surfactant inactivation [18]. Because surfactant inactivation plays such a crucial role in its pathophysiology, surfactant therapy is thought to improve oxygenation in MAS patients by improving the endogenous pool of surfactant and lung mechanics [19, 20]. The idea to use surfactant for MAS originated from in vitro and in vivo studies in which meconium was noted to inhibit surfactant activity in a dose-dependent fashion and this was improved with exogenous surfactant [19–22] also in a dose-dependent fashion. A retrospective study by Halliday et al. examined the effect of poractant alfa in 54 MAS patients and found that 66% of infants had a good to modest response with improvement in median arterial to alveolar oxygen tension ratio (a/A ratio) within one to two hours of treatment with 28-day survival of 81% [23].

Two important randomized clinical studies for surfactant use in MAS were published in 1996 and 1998 [24, 25]. In the RCT by Findlay et al., 20 infants with severe MAS received up to four doses of beractant every 6h [24, 25]. PPHN had resolved in all but one infant in the surfactant-treated group, with no air leak syndrome (compared to 5/20 in the control group), shorter duration of mechanical ventilation, oxygen therapy, and hospitalization compared to the placebo group [24]. Lotze et al. concluded similarly encouraging results after performing a multicenter ($n = 44$), randomized, double-blind, placebo-controlled trial with a larger sample size ($n = 328$), including

Table 1. Commercially available surfactants: composition and FDA approval criteria.

Name of Surfactant	Dose	Frequency	Derivation	Phospholipid per dose	Main Phospholipid	Proteins
Beractant (Survanta)	4 ml/kg	Every 6 h (First 48 h)	Bovine Minced Lung extract	100 mg/kg	DPPC and PG	(<0.1%) SP – B and (1%) SP – C
Calfactant (Infrasurf)	3 mL/kg	Every 6 to 12 h (First 72 h	Bovine calf lung lavage extract	105 mg/kg	DPPC and PG	(0.7%) SP – B and (1%) SP – c
Poractant alfa (Curosurf)	2.5 mL/kg (1st dose) 1.5 mL/kg (2nd/3rd doses)	Every 12 h With up to 2 repeat doses	Porcine minced lung extract	100–200 mg/kg 100 mg/kg	DPPC and PG	(0.6%) SP – B and (1%) SP – C
Lucinactant (Surfaxin)	5.8 mL/kg	Every 6 h up to 4 doses (First 48 h)	Synthetic	175 mg/kg	DPPC and POPG	KL4 peptide as SP-B

DPPC Dipalmitoyl phosphatidylcholine, *PG* Phosphatidylglycerol, *POPG* Palmitoyloleylglycerol.

Table 2. Summary of randomized controlled trials (RCTs) for Surfactant Lavage use in meconium aspiration syndrome (MAS) infants.

Study, Year published, sample size	Type of Surfactant, dose, and Frequency	Eligibility Criteria for randomization	Outcome
Wiswell et al. [30] (n = 22)	Lucinactant	Diagnosis of MAS, Birth GA ≥ 35, the requirement of mechanical ventilation, PMA ≤ 72 h, OI ≥ 8 and ≤25	Infants treated with surfactant lavage had fewer days of mechanical ventilation (6.3 vs. 9.9) and sustained improvement in oxygenation compared to the control group; however, this was not statistically significant.
	- 1st two doses of 2.5 mg/mL diluted in NS with a total of 8 mL/kg in each lung		
	-Third dose of 10 mg/mL diluted in NS with a total of 8 mL/kg in each lung		
	- Total three doses		
Dargaville et al. [31] (n = 66)	Beractant	Diagnosis of MAS, Birth GA ≥ 36, BW ≥ 2 kg, PMA < 24 h, requirement of mechanical ventilation with MAP ≥ 12 cm H_2O and two sequential blood gases with an alveolar-arterial oxygen difference of at least 450 mm Hg.	There was no difference in duration of respiratory support requirement, need for high-frequency ventilation, or iNO between infants who received surfactant lavage and standard of care treatment.
	- 5 mg/mL diluted in NS with a total of 15 mL/kg		Infants who received surfactant lavage had lower mortality or need for ECMO than the control group (10% vs. 31%).
	- Two doses		
Arayici et al. [33] (n = 33)	Poractant	Diagnosis of MAS, Birth GA ≥ 36, BW ≥ 2 kg, PMA < 24 h, requirement of mechanical ventilation with MAP ≥ 12 cm H_2O, OI >15	There was no difference in the duration of oxygen therapy, high-frequency ventilation, and iNO requirement between infants who received surfactant lavage and those who received bolus surfactant. There was also no difference in mortality or ECMO requirement between the two groups.
	Lavage Group:		
	- 5 mg/mL diluted in NS with a total of 15 mL/kg		
	- Two doses		
	Bolus Group:		
	- 100 mg/kg per dose		
	- Maximum of 2 doses		

MAS Meconium aspiration syndrome, *NS* normal saline, *GA* gestation age, *PMA* postmenstrual age, *OI* Oxygenation Index, *BW* Birth weight, *MAP* mean airway pressure, *iNO* inhaled nitric oxide, *ECMO* Extracorporeal membrane oxygenation.

patients with MAS ($n = 168$), sepsis and idiopathic PPHN [25]. While their data were not stratified by primary diagnosis, investigators observed that surfactant was effective in MAS and sepsis but not with idiopathic PPHN. They concluded that the use of surfactants in the early phase of these disorders decreased the need for ECMO without any increase in complications [25]. In a recent RCT by Chinese Collaborative Studies, improved oxygenation was again noted in neonates with MAS who were treated with poractant alfa within 36 h of age compared to the placebo group at 24 h, 3 days and 7 days post-treatment without major complications [26]. A post-hoc analysis of the early iNO in term HRF trial by Konduri et al. [27] showed that ECMO/death was 14% in the surfactant-treated HRF patients with perinatal aspiration syndrome and 30% among those not treated with surfactant (p-0.04). In 2012, Peter D'Argaville recommended surfactant as a standard therapy for neonates with severe MAS [17]. The 2014 Cochrane review evaluating surfactant for MAS in term and late preterm infants concluded that surfactant administration in infants with MAS may reduce the severity of respiratory illness and decrease the incidence of progressive respiratory failure and ECMO [28].

Surfactant lavage for MAS

Surfactant lavage is a procedure in which dilute surfactant is instilled into the lungs and subsequently removed via suctioning, thereby "cleansing" the lungs of particulate matter and coating the lungs with surfactant. The use of surfactant lavage is also not FDA-approved. Studies evaluating surfactant lavage have been most successful in MAS. It was first described in 1996 in two patients with severe MAS, for whom a large volume of saline was instilled prior to giving a bolus dose of surfactant. They noted that these patients had significant clinical improvement and good tolerance of the procedure [29]. Since then, several case reports, observational studies, RCTs (Table 2), and one meta-analysis describing the use of surfactant lavage in MAS have been published.

The first RCT designed as a pilot safety study included 22 infants ≥35w GA with MAS who needed mechanical ventilation with an oxygenation index (OI) of 8–25 [30]. The treatment group ($n = 15$) received lucinactant diluted with normal saline. Infants in the treatment group were weaned off mechanical ventilation earlier than placebo ($n = 7$, randomized 2:1); however, this was not statistically significant. The treatment group tolerated the procedure well, and there was no difference in ECMO or death between the two groups.

One of the major RCTs by Dargaville et al. was an international multicenter RCT that included 20 centers and 66 patients [31]. The intervention group received dilute beractant (1 in 5 dilutions with normal saline), and the control group received standard treatment, including high-frequency ventilation, nitric oxide and/or ECMO in centers where available. They noted no differences in the duration of respiratory support required, the need for high-frequency ventilation, and the need for iNO. Mortality or need for ECMO was significantly lower in the surfactant lavage group (10%) compared to the control (31%). The treatment group did have a transient decrease in oxygen saturation; however, they tolerated the procedure well. They concluded that while there may not be a significant improvement in respiratory status with surfactant lavage compared with standard treatment, it may improve mortality in centers where ECMO is not offered [32].

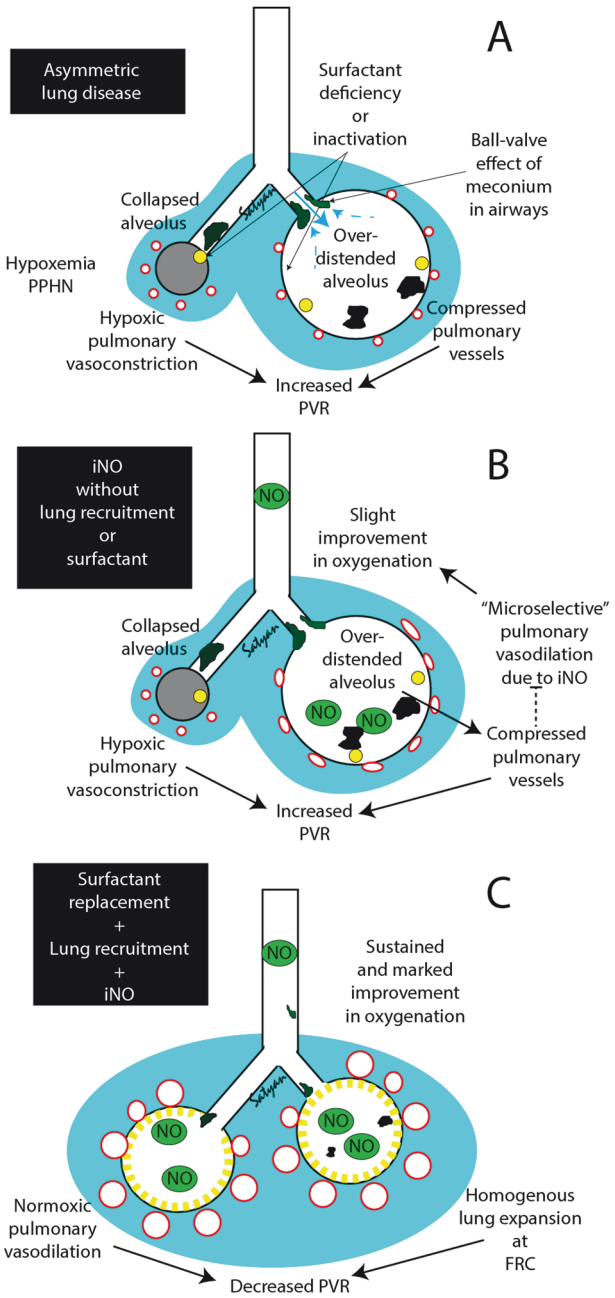

Fig. 1 Benefits of surfactant and lung recruitment prior to initiation of iNO. A In neonatal parenchymal lung disease such as meconium aspiration syndrome (MAS), surfactant deficiency or inactivation leads to asymmetric alveolar expansion. Due to LaPlace's law, the absence or deficiency of surfactant (small yellow circles in the alveolus) result in higher pressure in smaller alveoli leading to collapse and larger alveoli with low pressure leading to overdistension and air-leak. Partial obstruction to airways leads to a ball-valve effect, allowing air to enter (solid blue arrow) but unable to exit (dashed blue arrow) contributing to overdistension. Collapsed alveoli enhances adjacent hypoxic pulmonary vasoconstriction increasing pulmonary vascular resistance (PVR). Overdistension compresses alveolar pulmonary vessels (small red circles surrounding the alveoli) contributing to high PVR. **B** Administering inhaled nitric oxide (iNO) to such an asymmetrically recruited lung results in minimal improvement as the gas cannot reach its target pulmonary resistance vessels. In the overdistended alveoli, even though iNO reaches the pulmonary vessels, mechanical compression of the alveolar vessels by the distended alveolus dampens the vasodilatory effect of iNO. **C** Administration of exogenous surfactant reduces surface tension and enables symmetric recruitment of alveoli, improving iNO access to target pulmonary vessels and reducing PVR. Modified from Goldsmith's Assisted Ventilation of the Neonate (copyright Satyan Lakshminrusimha, used with permission).

A small RCT performed in Turkey by Arayici and colleagues examined the difference between surfactant lavage and bolus surfactant in MAS with a small sample size of 33 infants [33]. They found no differences in the duration of respiratory support, oxygen therapy, iNO, and incidence of death or ECMO between infants who received surfactant lavage and bolus surfactant. Surfactant lavage seems to be effective in removing particulate meconium; however, based on the current evidence, the benefits of surfactant lavage may be limited to resource-poor areas where ECMO is unavailable to improve mortality [31].

Pneumonia/sepsis

Inflammation and exudative material containing plasma proteins including cytokines can inactivate endogenous surfactants in infants with pneumonia leading to respiratory failure [34]. The RCT by Lotze et al. discussed earlier included infants with pneumonia/sepsis. While there was a 40% decrease in the need for ECMO for surfactant-treated infants in this study, the overall sample size of infants with sepsis/pneumonia specifically was small (50/167) and the study was not designed to detect differences within subgroups of neonates with different etiologies of respiratory failure [25]. Herting et al. retrospectively evaluated the use of surfactants in premature and term infants with group B streptococcus (GBS) infection and matched them with infants who had received surfactants for RDS. The investigators concluded that surfactant improved gas exchange in most infants with GBS pneumonia, but infants with GBS were slower to respond than infants with RDS alone and were more likely to need a repeat dose of surfactant [35]. They also noted a higher incidence of complications such as pneumothorax and IVH in the pneumonia/sepsis group compared to the RDS group. However, the groups were not matched for respiratory severity, and it is also possible that infants with GBS infection tend to be sicker than infants with RDS alone, and their respiratory failure is more complicated than simply lack of surfactant maturation [35].

Deshpande et al. prospectively evaluated surfactant use in 24 late preterm to term infants with early onset pneumonia to assess the effect on gas exchange and oxygenation. They found a significant improvement in oxygenation index (OI) at one hour (11.5 to 3.7) and this improvement was sustained at 12 hours post-surfactant [36]. In this study, only six out of 24 infants had proven pneumonia with positive culture and the remaining infants met clinical criteria for pneumonia. It is possible that some infants just had RDS confounding the results in favor of the use of surfactant to treat pneumonia. More recently, Rong et al. published a multicenter RCT to evaluate the effect of bovine surfactant on neonatal acute respiratory distress syndrome (NARDS) due to pneumonia in infants greater than 34w gestation [37]. The OI was significantly improved in surfactant-treated infants compared with the placebo group at four and 12 h after treatment. However, there was no difference in OI by 24 h after treatment between the two groups along with duration of ventilator and oxygen, mortality, or major morbidity. Infants with pneumonia in the Lotze et al. multicenter trial [25] and in the post-hoc analysis of early iNO trial by Konduri et al. showed a significant reduction in ECMO or ECMO/death [27]. In babies with parenchymal lung disease and PPHN, iNO is more effective when surfactant is used (Fig. 1) to optimize lung

recruitment as it allows more effective diffusion of iNO from alveoli to capillaries. Gonzalez et al. randomized 100 term newborns with acute HRF (OI ≥ 20) to iNO plus up to two doses of surfactant vs. iNO + placebo [38]. Infants receiving iNO with surfactant improved their oxygenation faster, resulting in a significantly lower OI at 24 h: 12.9 ± 9 vs 18.7 ± 11 of controls, $p < 0.05$, and the treated group had a lower primary outcome of severe HRF (OI > 40) (24% vs 50% of controls, $p < 0.02$) and had a lower risk of the combined outcome of death or ECMO: 16% vs. 36%, $p < 0.05$.

In summary, surfactant treatment may offer acute improvement of respiratory symptoms in infants with pneumonia or sepsis; however, data are lacking to suggest routine use of surfactant to improve long-term outcomes. Despite that, we recommend that early exogenous surfactant treatment should be considered in term or near-term infants with pneumonia or sepsis with severe respiratory failure, requiring significant supplemental oxygen after optimization of medical and ventilator management to avoid more invasive therapies such as ECMO and its associated complications. A recent 2019 consensus statement by the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) recommended using surfactant in neonates with PPHN and pulmonary diffusion impairment (but without CDH) [39]. Several trials of surfactant in adult ARDS have not been successful [40–43]. Thus, further understanding of the mechanism of action of surfactant inadequacy in term infants will likely improve our understanding of the management of surfactant use in patients of all ages.

Congenital diaphragmatic hernia (CDH)

CDH is associated with pulmonary hypoplasia and pulmonary hypertension. CDH lungs are significantly less compliant than normal lungs, however, the role of surfactant in the pathophysiology of CDH is controversial. In the 1990s, a series of ovine studies suggested CDH-associated lung developmental changes that could be improved with exogenous surfactant [44, 45] Despite the success of surfactant administration in this model, human studies remain less convincing. It is unclear if CDH patients have primary surfactant deficiency or an alteration in surfactant function due to positive pressure ventilation or high oxygen content. In a case report, Bae noted improved lung volume and gas exchange in an infant who received surfactant after surgical repair [46]. However, in a small RCT by Lotze et al., there was no difference noted in lung compliance, duration of ECMO, oxygen requirement, or duration of oxygen need in neonates with CDH requiring ECMO who were treated with surfactant compared to air (placebo) [47]. In a large retrospective study of infants followed by the CDH registry, 192 infants with CDH who received surfactant were compared with 330 control CDH infants with similar clinical profiles. Infants in the surfactant treatment group had higher use of ECMO, higher incidence of chronic lung disease, and higher mortality rate compared to control [48]. Because of the retrospective nature of the study, it cannot be concluded that surfactant administration leads to worse outcomes in CDH infants. It is likely that sicker infants with CDH received surfactant. Nothing short of a multicenter RCT will be able to inform this question for this complex and relatively rare group of patients. We do not recommend the use of surfactant in CDH unless the infant is premature, and the lung fields show signs of RDS.

PREMATURE INFANTS AFTER 72 HOURS: THE "POST-SURFACTANT SLUMP"

In some premature infants, the course of RDS may be prolonged due to its severity or delayed surfactant system maturation at 3–7 days of age, or the respiratory status may worsen (e.g., due to ventilator-induced lung injury) outside the window of FDA-approved postnatal age (<72 h) for surfactant replacement therapy. Delayed maturation of the surfactant system and post-surfactant slump was first described in 1994 by Sobell and Caroll as worsening of respiratory failure in premature infants in the second postnatal week following a good response initially to early surfactant for RDS [49]. This post-surfactant slump may be due to surfactant dysfunction from mechanical ventilation, pulmonary edema, inflammation, atelectotrauma, oxidative stress, and/or infection [50]. Theoretically, using exogenous surfactant during this period could be beneficial to improve lung mechanics. However, limited evidence exists for its efficacy and safety to support the use of surfactants in premature infants after 72 h. Small RCTs and observational studies have described late surfactant use in premature infants with worsening respiratory failure (Table 3) [51–53]. Regardless of the lack of significant RCT evidence for late surfactant use, in the large NIH Prematurity and Respiratory Outcomes Program (PROP) cohort, 7.2% of 832 babies who were <29 w gestation received surfactant after 72 h of age; this was the highest at 14.1% in babies of 23 to 24 w GA and lowest at 2.6% in babies born at 27 to 28w GA [11]. Clearly, there is an increase in off-label surfactant use, particularly in low gestational-age infants.

Observational Studies for the use of surfactant in premature infants after 72 hours

In 1995, Pandit et al. prospectively studied 10 infants with a median birth weight of 693 g and median birth gestation of 25w who required persistent mechanical ventilation with a fraction of inspired oxygen (FiO_2) > 0.4 at 7 to 30 days of age [54]. After a dose of surfactant, there was a significant improvement in the ventilator efficiency index at 24 to 48 h post administration and a decrease in FiO_2 [54].

Katz and Klein from the Iowa group, known for their high survival in babies with birth weight <500 grams, reviewed 165 extremely low birth weight infants admitted to their institution and receiving late surfactant between 1999 to 2001 [10]. In this study, the infants were categorized into three groups: infants who received no surfactant, infants who received early surfactant only (RDS) and infants who received early and late surfactant (for RDS and post-surfactant slump). Post-surfactant slump and the need for late surfactant was based on respiratory failure after 6 days of age defined as FiO_2 requirement >0.70 on HFV. Infants who received late surfactant were significantly more premature and had lower birth weights than the other two groups. In addition to earlier gestational age, lack of antenatal steroids, and the need for 2 or more surfactant doses for RDS were identified as risk factors for needing late surfactant therapy for post-surfactant slump. Of the 25 infants treated with late surfactant, 18 patients had improvement in their respiratory severity score by 15% when measured at 12, 48 and 72 h post late surfactant administration. Interestingly, the infants who received late surfactant had the same incidence (84%) of BPD as infants who received early surfactant only; the incidence was lower in infants who didn't require any surfactant. In addition, late surfactant may or may not be the reason for this group's success with ELBW infants since it is a single center, and these clinicians may be employing other management strategies that are more impactful.

Recently, in a Pediatrix cohort of ~718,000 babies born < 37w GA from 1997–2017, 4% received surfactant after the FDA-approved postnatal age [55]. In this retrospective analysis, authors characterized the use, efficacy, and safety profiles of calfactant and poractant alfa compared to beractant when used post FDA approved age. Infants received late surfactant at a median postnatal age of eight days with an interquartile range of 3–22 days. There was a steady decrease in total surfactant

Table 3. Summary of Literature for Late Surfactant Use in Premature Infants.

Study, year published, and Type of Study	Timing of late surfactant	Criteria for use of late surfactant	Outcome	Long term outcome
Pandit et al. [54, 63] Prospective	7 to 30 days of age	FiO_2 of > 0.4 with BW < 1500 g with stable ventilatory requirement without PDA, active infection, or current steroids	Improvement in ventilator efficiency index at 24 to 48 h post surfactant administration	Not assessed
Katz and Klein, [10], Retrospective Chart review	After 6 days of age (Median age 11 days)	Infants with BW < 1000 g with FiO2 > 0.7 for >6 to 8 h despite optimizing HFV	Improvement in RSS score at 12, 24 and 48 h post instillation	Not assessed
Laughon et al. [51], Masked, multicenter, multinational, pilot RCT	3–20 days of age	Infants with BW between 600–900 g requiring mechanical ventilation with FiO2 > 0.3	There were trends toward decreased O_2 requirement and lower rate of death or BPD at 36w PMA, not statistically significant	Not assessed
Ballard et al. [53] (TOLSURF Study), Multicenter, masked RCT	7 to 14 days of age Up to 5 doses of surfactant if meeting criteria	Infants ≤28 0/7w gestation requiring mechanical ventilation and as a part of study, all infants received iNO	No difference in survival without BPD at 36 or 40 weeks	At 1-year corrected age, late surfactant group had decreased use of home respiratory support
Hascoet et al., 2016, Multicenter, double-blinded RCT	14 days of age	<33w gestation at birth with FiO2 requirement of >0.3.	Late surfactant treated group had improved FiO_2 for up to 24 h after instillation, however no difference noted in rate of BPD or death at 36w PMA	Late surfactant group had decreased respiratory morbidity measured as decreased hospitalization for respiratory problems prior to 1 year of age.

BW Birth weight, *HFV* High Frequency Ventilation, *RSS* Respiratory severity score, *BPD* Bronchopulmonary dysplasia.

administration starting in 2007, but late surfactant administration increased over time, peaking in 2017. There was no significant difference among the type of late surfactants used on air leak syndrome, BPD, or all-cause death. In addition, infants between 33–36w GA who received off-label poractant alfa were noted to have significantly more safety events (defined as hemodynamic instability, respiratory deterioration, sepsis, pulmonary hemorrhage, death within three days) compared to infants who received calfactant or beractant. Without data from a formal RCT, pre- and post-physiology data might be the most useful to report in anecdotal reports at this time.

Randomized Controlled trials for the use of surfactant in premature infants after 72 hours

In 2016, a large masked RCT called Trial of Late Surfactant (TOLSURF) studied up to five doses of calfactant every other day in infants ≤28w gestation who remained on mechanical ventilation at 7–14 days of age; the study showed no benefit of death/BPD at 36w PMA [53]. All infants were also treated with prolonged iNO which may have affected the results. Of interest, when this group reported one-year respiratory outcome, fewer infants in the booster surfactant group required home respiratory support compared with control infants [56]. Hascoet et al. performed a double-blinded RCT at 13 French perinatal centers to evaluate the efficacy of late surfactant administration on day 14 in infants < 33w GA at birth who were on mechanical ventilation with inspired oxygen of more than 0.3 [52]. In their study population of 118 infants, there was statistically no difference in the primary outcome of ventilation duration in control and the late surfactant administered group. However, the treated group had a significantly decreased rate of hospitalization (28.3%) for respiratory problems post discharge compared to the control group (51.1%). Interestingly, this was remarkably similar for the TOLSURF study, which showed decreased later respiratory morbidity outcomes in the late surfactant group [56]. With two RCTs suggesting a post-discharge advantage with late doses of surfactant, late surfactant can be considered a research gap for future studies. Perhaps late surfactant offers a period of lung protection during a particularly vulnerable window of lung development, affecting later lung function and associated with less respiratory morbidity post-discharge. In contrast, a multicenter pilot RCT by Laughon and colleagues showed a significant reduction in supplemental oxygen requirement and BPD or death in their study population treated with a standard dose of a newer non-animal-derived surfactant, lucinactant, every 48 h for five doses if they remained intubated, compared with the placebo group [51].

The use of late off-label surfactants may be evolving as a research question as we gain more data, but late surfactant administration in premature infants is not yet routine practice. However, we have clear evidence from Merrill et al. and Keller et al. that premature babies on mechanical ventilation at 2–11 weeks of age have surfactant deficiency with tracheal aspirate showing higher minimum surface tensions and lower concentrations of SP-B when they have respiratory exacerbations or bacterial infections and that exogenous surfactant in the TOLSURF trial did increase tracheal aspirate SP-B levels [57, 58]. These data suggest that there may be some “acute” surfactant inadequacy on top of chronic insufficiency in some ventilated premature infants. We do not know the etiology of this inadequacy, but it is an understudied area from a basic surfactant biology understanding.

In summary, there is inadequate evidence to support the off-label use of surfactants to improve respiratory outcomes in premature infants after 72 h of age. It may reduce long-term respiratory-related morbidities for extremely low gestational age infants; however, more evidence is needed to provide more

specific recommendations for this group to use late surfactant administration. These studies had a consistent theme: infants with lower gestational age and birth weight were more likely to have respiratory decompensation after 3 days. With the increased trends in the resuscitation of extremely low gestational-age infants, there is still more to be learned about how hemodynamic changes may also affect HRF in these populations over time. For example, the Iowa group recently reported that neonates with gestational age <27w without PDA were more likely to respond positively to late surfactant than infants with PDA [59].

Pulmonary hemorrhage. Pulmonary hemorrhage or hemorrhagic pulmonary edema is occasionally seen in preterm infants with a large PDA. Blood inhibits surfactant function in vitro [34, 60]. Hence, the exogenous surfactant can be used as a rescue medication to improve pulmonary mechanics in the setting of a clinically significant pulmonary hemorrhage [61]. However, there is limited evidence for this, with only a few retrospective or observational studies reported to date that have shown benefits for the use of surfactants in pulmonary hemorrhage in premature infants [62–64]. More studies are needed to understand the effectiveness of surfactant therapy for clinically significant pulmonary hemorrhage. In addition, there are uncertainties about how often and what dose of surfactant should be given, and if surfactant could worsen pulmonary hemorrhage by increasing pulmonary blood flow through PDA.

Surfactant as drug delivery vehicle: Bronchopulmonary dysplasia continues to remain the most frequent morbidity of prematurity. The exact pathophysiology of BPD is unknown, but inflammation in developing lungs causing oversimplification of alveoli is thought to be one of the major reasons [65]. Steroids have been shown to improve the risk of BPD [66]. However, the use of systemic steroids can cause undesired side effects [67], limiting its use to later PMA when the inflammatory damage in the lungs may not be reversible. Yeh et al. described mixing budesonide with surfactant to deliver steroids in more distal airways to improve the efficacy of steroids in local regions to improve respiratory outcomes while potentially minimizing systemic side effects [68]. In this RCT, 265 very low birth weight (<1500 g) infants with severe RDS were enrolled [68]. The infants that received surfactant with budesonide had a significantly lower incidence of BPD than those that received surfactant alone. A recent observation study by Kothe et al. described a change in their unit practice to improve the rate of BPD locally by using surfactant with budesonide in all of their infants that required intubation for RDS [69]. They compared infants who received surfactant and budesonide with infants from previous years who received surfactant alone for RDS. In their unit, there was no change in the incidence of BPD with this practice change; however, the severity of BPD decreased. There is limited data currently on extremely premature infants with earlier stages of lung development and infants with mild RDS to recommend routine use of surfactant with budesonide to improve the risk of BPD. There are multicenter RCTs such as BiB (NCT04545866) and PLUSS [70] underway to evaluate the risk of developing BPD and the long-term effects of infants treated with budesonide and surfactant compared to surfactant alone for RDS. Findings in these studies will be able to answer more questions to allow further recommendations of using budesonide with surfactant in this vulnerable group. Until these studies are completed, this should not be considered routine practice.

ALTERNATE METHODS OF SURFACTANT DELIVERY

Most studies pertaining to surfactant therapy in term infants are based on intratracheal delivery through an endotracheal tube. As less-invasive methods of surfactant administration such as using a small angiocath or feeding tube (Less-Invasive Surfactant Administration (LISA), also called Minimally Invasive Surfactant Administration (MIST)), using brief intubation/extubation (**IN**tubation-**SUR**factant-**E**xtubation (INSURE)), a laryngeal mask airway (LMA) or aerosolization have become widely available in preterm infants [71, 72], we may see an increase in alternate modes of surfactant administration in term infants as well. More investigation is needed to accurately diagnose surfactant deficiency and examine how this information can be applied in a clinical setting to improve respiratory outcomes for term infants. While early and/or perfunctory surfactant use is most evidence-based for premature infants and infants with MAS, the evidence is less abundant for other disease processes specifically in term infants. It is also important to recognize that studies to date for term infants have used surfactants primarily in infants who required mechanical ventilation. The advent of non-invasive surfactant treatment will change our practice, and new studies will be needed.

Biological assessment for surfactant deficiency or inactivation

There is currently no clinical consensus on diagnosing an infant with surfactant deficiency or inadequacy. Once diagnosed, the criteria for using exogenous surfactant in these infants varies among practice sites and providers. Diagnosis of surfactant deficiency via microbubble stability test using amniotic fluid, gastric or tracheal aspirate has been described in both premature and term infants [73–76]. While the microbubble stability test may be helpful, it has been validated in only small sample studies, making it difficult to standardize. Recently, Autililo et al. studied term and preterm infants using a surfactant adsorption test to study surfactant adequacy; they were able to predict failure of continuous positive airway pressure (CPAP) and the need for surfactant replacement in <32w gestational age infants with RDS [77]. The surfactant adsorption test measures phospholipid surface film formation in multiwall plates with fluorescence-labeled surfactant and a light quencher that allows high-throughput kinetic analysis at various concentrations of surfactant [78]. While more evidence is needed, including data in term infants and larger patient samples, this technique could potentially be standardized and used for clinical applications.

Accurate identification of surfactant deficiency in an individual baby would allow for a more individualized approach to treating infants with exogenous surfactants than a generalized protocol for HRF for all infants. There may even be an opportunity to look at SP-B levels, which is associated with lower minimum surface tension [57]. However, using standard lab techniques for measuring a specific protein will take hours, making it impractical for use clinically.

IN CONCLUSION

Surfactant is the standard of care in premature infants with RDS with strong evidence over many years. In addition, sufficient evidence supports the use of surfactants in term infants with MAS or pneumonia/sepsis to prevent the need for ECMO. There is some evidence, albeit limited, to support use of surfactant for severe neonatal HRF due to other lung diseases (Fig. 2). More studies are needed to understand long-term outcomes of term infants treated with surfactant for HRF. Current RCT data does not support routine use of surfactant for premature infants beyond 72 h for “post surfactant slump” to improve respiratory outcomes (Fig. 2). Some observational cohort data do suggest that late surfactant could be advantageous in extremely premature infants to improve long term respiratory morbidity. It would be useful to develop a bedside-friendly rapid assessment tool for surfactant inadequacy that could be used throughout the NICU course, which then could be used to select patients more appropriately for future RCTs.

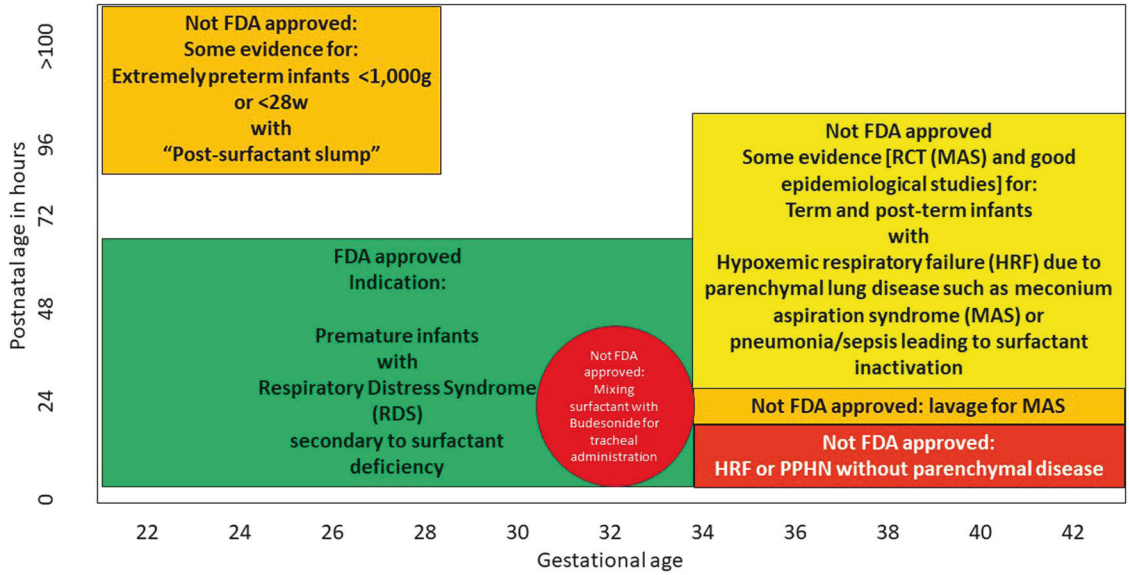

Fig. 2 Evidence and FDA approval behind the use of exogenous surfactant for different diagnoses, for a given gestational age (horizontal axis) and postnatal age in hours (vertical axis). FDA approved indication (Green box): There is sufficient evidence to recommend use of exogenous surfactant for respiratory distress syndrome (RDS) in extremely premature to late preterm infants within 72 hours post menstrual age (PMA). **Evidence-based, but not FDA approved (Yellow box):** There is adequate evidence to support early use of surfactant in late-preterm or term infants with severe hypoxic respiratory failure due to lung disease such as meconium aspiration syndrome (MAS), pneumonia/sepsis to prevent need for ECMO and subsequent complications. **Not FDA approved (Orange Box, top left):** There is very limited evidence to support routine use of exogenous surfactant in premature infants with hypoxic respiratory failure after 72 hours PMA. **Not FDA approved (Orange Box, bottom right):** Surfactant lavage is not approved by FDA, however when performed by experienced team, it may help to reduce mortality in a unit in which ECMO is not offered. **Not FDA approved, not evidence based (Red box):** Surfactant is not approved and, based on current evidence, it is contraindicated for infants with persistent pulmonary hypertension without lung disease, and congenital diaphragmatic hernia without lung disease. **Not FDA approved (Red circle):** Surfactant mixed with budesonide for treatment of RDS to improve long-term respiratory outcomes is not FDA approved and we do not have sufficient evidence to recommend its use routinely.

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AUTHOR CONTRIBUTIONS

RMR provided the leadership, senior directorship, and the review outline and concept. HA, RKD and SL contributed to the drafting, reviewing, and revision of the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. SL contributed the figures.

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ADDITIONAL INFORMATION

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