Lung Diseases: Surfactant Replacement Therapy in Newborns

63

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Contents

Abstract

In the past three decades, introduction of prenatal steroid treatment, postnatal surfactant therapy, and assisted ventilation has contributed to better outcomes for neonates with respiratory distress syndrome (RDS). Improved survival is directly related to more effective prevention or treatment of the disease. RDS is caused by surfactant insufficiency leading to alveolar collapse and increased work of breathing with consequent hypoxia, respiratory failure, and mixed respiratory and metabolic acidosis. Following unsuccessful clinical trials in the 1960s with nebulized synthetic surfactants, comprised of phospholipids without surfactant proteins, a number of randomized controlled trials in the 1980s demonstrated benefits of surfactant instilled directly into the lungs of preterm infants. Currently, because of increased use of prenatal steroids and early

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CPAP, it is clear that early selective use of surfactant is superior to routine prophylactic treatment. However, there are still some occasions when surfactant should be administered in the delivery room including cases when intubation of very preterm infants is needed for stabilization.

63.1 Salient Points

- Respiratory distress syndrome is caused by surfactant insufficiency which leads to progressive hypoxia, respiratory failure, and mixed respiratory and metabolic acidosis as a result of alveolar collapse and increased work of breathing.
- The use of prenatal steroids and early CPAP make early selective use of surfactant superior to routine prophylactic treatment. There are still some occasions when surfactant should be administered in the delivery room including cases when intubation of very preterm infants is needed for stabilization.
- The dose of surfactant required for optimal effects is not known. It is possible that 100 mg/kg is sufficient for prophylactic treatment, but 200 mg/kg may give better outcomes for the later treatment of RDS.
- The INSURE (INtubateSURfactant Extubate to CPAP) technique minimizes the duration of ventilation and is useful for babies initially treated with CPAP who may avoid mechanical ventilation altogether.
- Less invasive surfactant administration (LISA) and nebulization are techniques that show promise and help to avoid endotracheal intubation.
- Other indications for surfactant include meconium aspiration syndrome (reducing the need for ECMO) and pneumonia, but in other cases the treatment is experimental.
- Surfactant may be used as a vehicle to deliver drugs to the lungs, and trials with budesonide show promise as a means of reducing bronchopulmonary dysplasia.

63.2 Introduction

In the past three decades, introduction of prenatal steroid treatment, postnatal surfactant therapy, and assisted ventilation has contributed to improved neonatal outcomes (Speer et al. 2013). Improved survival is directly related to more effective prevention or treatment of respiratory distress syndrome (RDS), which prior to the 1990s had a high mortality. Following unsuccessful clinical trials with nebulized synthetic surfactants, comprised of phospholipids without surfactant proteins, in the 1960s (Soll 2000a) a number of randomized controlled trials in the 1980s demonstrated benefits of surfactants instilled directly into the lungs of preterm infants (Soll 2000a, b; Seger and Soll 2009; Soll and Ozek 2010). These surfactants were of two main types: natural (derived from animal lungs or human amniotic fluid) (Soll 2000a; Seger and Soll 2009) containing surfactant proteins B and C (SP-B and SP-C) and synthetic (Soll and Ozek 2010; Soll 2000b) (containing phospholipids and other agents to facilitate spreading and adsorption). Both types of surfactant, given either prophylactically (in the delivery room within 15 min of birth) (Soll 2000a; Soll and Ozek 2010) or for treatment of RDS (Seger and Soll 2009; Soll 2000b), increased neonatal survival and reduced pulmonary air leaks such as pneumothorax and pulmonary interstitial emphysema.

More recently, further randomized clinical trials helped determine the best surfactant (Pfister et al. 2007, 2009; Ardell et al. 2015), the optimal timing for initial treatment (Singh et al. 2015; Rojas-Reyes et al. 2012; Bahadue and Soll 2012; Stevens et al. 2007), the need for redosing (Soll and Ozek 2009), and the dose of phospholipids needed for best outcomes (Speer et al. 2013). Results from these trials have provided guidelines for best practice, and these are now available in Europe (Sweet et al. 2013), the USA (Polin et al. 2014), and Canada (Davis et al. 2005). The aim of this chapter is to summarize the recommendations for surfactant treatment based on evidence from clinical trials and systematic reviews and to point out areas where controversy still exists.

63.3 Respiratory Distress Syndrome and Rationale for Surfactant Therapy

Respiratory distress syndrome (RDS) is caused by surfactant insufficiency (Avery and Mead 1959) which leads to progressive hypoxia, respiratory failure, and mixed respiratory and metabolic acidosis as a result of alveolar collapse and increased work of breathing (Halliday 2003). Surfactant deficiency is strongly associated with prematurity, and progressive acidosis further reduces surfactant production. The normal surfactant phospholipid pool size at birth is about 100 mg/kg, but in preterm infants this is often reduced to below 25 mg/kg, and if severe RDS is present, less than 5 mg/kg (Halliday 2003). Surfactant may also be inactivated by leaking of inhibitory proteins from the plasma into the alveoli. Prior to introduction of surfactant therapy, infants with RDS who survived began to produce their own endogenous surfactant after 2–3 days, and this heralded their recovery (Halliday 2003). Those infants who did not survive either developed progressive respiratory failure with irreversible hypoxic injury to the cardiovascular and central nervous systems or acute deterioration associated with pulmonary air leaks or intraventricular hemorrhage.

Surfactant therapy prevents or overcomes alveolar collapse, especially at end expiration, increases lung volumes and pulmonary compliance, and reverses respiratory failure (Halliday 2003). The result is improved survival and significant reduction in pulmonary air leaks following surfactant treatment (Soll 2000a, b; Seger and Soll 2009; Soll and Ozek 2010). There is evidence from both animal studies and clinical trials that natural surfactants, containing SP-B and SP-C, act more rapidly than synthetic preparations containing mainly phospholipids, leading to improved outcomes with regard to survival and pulmonary air leaks (Pfister et al. 2007; Ardell et al. 2015). There may also be differences when natural (animal-derived) surfactants are compared (Singh et al. 2015). Timing of surfactant therapy may also be important in determining outcome with evidence pointing to earlier therapy being superior to later treatment (Rojas-Reyes et al. 2012; Bahadue and Soll 2012). However, with increased use of prenatal steroids and early CPAP, prophylactic surfactant treatment may not be superior to delayed selective treatment (Rojas-Reyes et al. 2012). The incidence of RDS varies from about 80% at 28 weeks' gestation or below to about 50% at 30 weeks, 30% at 32 weeks, and 10% at 34 weeks (Halliday 2003).

63.4 Results from Randomized Trials and Systematic Reviews

These are discussed under the following subheadings: efficacy, timing of first dose, size of first dose, method of administration, need for redosing, type of surfactant, concomitant interventions, and other indications for surfactant therapy.

63.4.1 Efficacy

Randomized clinical trials of synthetic (protein-free) and natural (containing SP-B and SP-C) surfactants, given both prophylactically (within 10–15 min of birth in the delivery room) or as treatment for established RDS in the neonatal unit, reduce neonatal mortality and pulmonary air leaks such as pneumothorax and pulmonary interstitial emphysema (Speer et al. 2013; Soll 2000a, b; Seger and Soll 2009; Soll and Ozek 2010). Although most of these trials took place in the 1980s and 1990s, when prenatal corticosteroid treatment was less frequent than today, there is no reason to believe that surfactant treatment does not continue to have a positive impact on the outcome of preterm infants (Speer et al. 2013). Indeed prenatal corticosteroids and postnatal surfactant have synergistic effects (Jobe et al. 1993), and both should be considered when preterm birth is likely. The sizes of the effects of prophylactic surfactant administration on neonatal mortality, pneumothorax, and other selected outcomes are shown in Table 1.

Table 1 Meta-analyses of prophylactic surfactant treatment of preterm infants

	Natural surfactant				Synthetic surfactant			
Outcome	RR	95% CI	NNT	95% CI	RR	95% CI	NNT/H	95% CI
Neonatal mortality	0.60	0.44–0.83	14	9–35	0.70	0.58–0.85	15	10–31
Pneumothorax	0.35	0.26–0.49	7	5–9	0.67	0.50–0.90	20	12–67
Pulmonary interstitial emphysema	0.46	0.35–0.60	6	4–8	0.68	0.50–0.93	16	9–77
Pulmonary hemorrhage	–	–	–	–	3.28	1.50–7.16	33	20–100
Intraventricular hemorrhage	0.89	0.84–1.15	–	–	0.96	0.81–1.14	–	–
Severe IVH	1.22	0.90–1.66	–	–	1.01	0.75–1.38	–	–
Persistent ductus arteriosus	1.08	0.94–1.24	–	–	1.11	1.00–1.22	21	11–500
Retinopathy of prematurity	1.37	0.63–2.98	–	–	0.96	0.86–1.07	–	–
Severe ROP	0.58	0.27–1.24	–	–	0.89	0.58–1.36	–	–
Bronchopulmonary dysplasia	0.93	0.80–1.07	–	–	1.06	0.83–1.36	–	–

Data obtained from Cochrane Library (Soll 2000a; Soll and Ozek 2010). *RR* relative risk, *CI* confidence interval, *NNT*/*H* number needed to treat or harm; *IVH* intraventricular hemorrhage, *ROP* retinopathy of prematurity, *BPD* bronchopulmonary dysplasia

63.4.2 Timing of First Dose

It is clear that the earlier surfactant is given in the course of RDS, the better the outcomes with reduction in pulmonary air leaks, neonatal mortality, and CLD (Bahadue and Soll 2012). In early trials of prophylactic surfactant in infants <31 weeks' gestation, neonatal mortality and pneumothorax were reduced compared to later treatment of established RDS (Rojas-Reyes et al. 2012). However, recent large trials that reflect current practice (including greater use of prenatal steroids and early stabilization with CPAP) do not support these benefits and show reduced risk of CLD or death when using early CPAP with selective surfactant administration for infants needing intubation (Rojas-Reyes et al. 2012). Administration of surfactant generally requires endotracheal intubation, and routine prophylaxis of infants <31 weeks' gestation might lead to unnecessary treatment in up to 50% of cases (Speer et al. 2013). This will increase costs of care and could cause unwanted lung injury leading to BPD. Currently, because of increased use of prenatal steroids and early CPAP, it is clear that early selective use of surfactant is superior to routine prophylactic treatment (Rojas-Reyes et al. 2012). However, there are still some occasions when surfactant should be administered in the delivery room including cases when intubation of very preterm infants is needed for stabilization (Sweet et al. 2013).

63.4.3 Size of First Dose

Clinical trials used surfactant doses ranging from 25 to 200 mg phospholipids/kg (Morley 1991). These doses are all much larger by at least tenfold than the amount of lipids needed to form a monolayer on the alveolar surface of the lungs (Robertson and Halliday 1998). For licensed surfactant preparations, the recommended doses vary from 50 to 200 mg/kg with dose volumes of 1.2–5 mL/kg (Table 2) (Sweet et al. 2013; Polin et al. 2014; Walsh et al. 2013). Larger doses of surfactant are superior to smaller ones (Konishi et al. 1988; Gortner et al. 1994). Surfactant TA in a dose of 120 mg/kg (100 mg phospholipids/kg) improved oxygenation and reduced BPD compared to 60 mg/kg (Konishi et al. 1988). When 100 mg/kg of bovactant was compared with 50 mg/kg, the larger dose was associated with better improvement in oxygenation (Gortner et al. 1994). For poractant alfa 200 mg/kg gives a better acute response than 100 mg/kg (Halliday et al. 1993; Ramanathan et al. 2004) and probably improved survival (Ramanathan et al. 2004). The

Table 2 Some surfactant preparations in clinical use

Generic name	Trade name	Source	Phospholipids (mg/mL)	Dose (mg/kg)	Volume (mL/kg)	Manufacturer (country)
Beractant	Survanta	Bovine mince	25 (50% DPPC)	100	4	Abbott Labs (USA)
BLES	bLES	Bovine lavage	27	135	5	BLES Biochemicals (Canada)
Bovactant	Alveofact	Bovine lavage	42	50	1.2	Lyomark Pharma (Germany)
Calfactant	Infasurf	Bovine lavage	35 (74% DPPC)	105	3	ONY and Forest Labs (USA)
Poractant alfa	Curosurf	Porcine mince	80 (70% DPPC)	100–200	1.25–2.5	Chiesi Farmaceutici (Italy)
Surfactant TA	Surfacten	Bovine mince	30 (48% DPPC)	120	4	Tokyo Tanabe and Mitsubishi Pharma (Japan)

All preparations contain SP-B and SP-C in varying amounts. *BLES* bovine lipid extract surfactant

dose of surfactant required for optimal effects is not known but is probably at least 100 mg phospholipids/kg which is close to the 100–250 mg/kg estimated to form the total pulmonary surfactant pool in a full-term neonate (Robertson and Halliday 1998; Hallman 1989). It is possible that 100 mg/kg is sufficient for prophylactic treatment (Speer et al. 2013), but 200 mg/kg may give better outcomes for later treatment of RDS (Ramanathan et al. 2004).

63.4.4 Method of Administration

Surfactants usually need to be administered directly into the lungs during at least a brief period of endotracheal intubation (Speer et al. 2013). Preterm infants at high risk of developing RDS should be born in centers where personnel and equipment are readily available to allow appropriate care to begin from birth (Sweet et al. 2013). In some of the earlier clinical trials, surfactant was administered as a bolus into each main bronchus or as a single bolus into the lower trachea, whereas in other trials it was given as divided doses directed into each lung lobe by positioning the baby (Morley 1991). After instillation the baby is either manually ventilated for a short time or reconnected to the ventilator to distribute the surfactant. A sterile feeding tube is often used to deliver the surfactant through the endotracheal tube. Bolus administration has been compared with infusion over 30 min in an animal model with the former giving more uniform distribution (Ueda et al. 1994). However, a small clinical trial with beractant found no differences in outcome when three dosing procedures were compared (Zola et al. 1993), and this was supported by a study with poractant alfa, which compared a bolus dose with a 1 min infusion through a dual lumen tube (Valls-i-Soler et al. 1998). It is important to minimize duration of mechanical ventilation after surfactant administration as this is an independent risk factor for development of BPD (Vento et al. 2009). The INSURE (INtubate SURfactant Extubate to CPAP) technique minimizes duration of ventilation and is useful for babies initially treated with CPAP who may avoid mechanical ventilation altogether (Bohlin et al. 2008). Although more surfactant is used with INSURE (RR 1.62, 95%CI 1.41–1.86), the benefits of reduced air leak (RR 0.52, 95%CI 0.28–0.96), BPD (RR 0.51, 95%CI 0.26–0.99), and need for mechanical ventilation (RR 0.67, 95%CI 0.57–0.79) (Stevens et al. 2007) mean that this technique is recommended (Sweet et al. 2013). The benefits appear to be even greater when infants are treated at a lower threshold oxygen requirement of less than 45% (Stevens et al. 2007).

Other methods to forgo the need for endotracheal intubation include nebulization (Berggren et al. 2000), direct tracheal instillation at laryngoscopy using a fine feeding catheter (Kribs

et al. 2008), intrapartum pharyngeal deposition (Kattwinkel et al. 2004), and use of a laryngeal mask (Trevisanuto et al. 2005). Of these, less invasive surfactant administration (LISA) is the most widely accepted (Kribs et al. 2008, 2015), but the technique needs considerable expertise and may not prove to be widely applicable (Speer et al. 2013). Studies with nebulization of surfactant are ongoing, and this technique shows promise (Pillow and Minocchieri 2012).

63.4.5 Need for Redosing

At least two studies demonstrated that multiple doses (up to three) are superior to a single dose (Dunn et al. 1990; Speer et al. 1992), and this is confirmed in a systematic review showing reduced pneumothorax (RR 0.51, 95%CI 0.30–0.88) and a trend toward reduced mortality (RR 0.63, 95%CI 0.39–1.02) (Soll and Ozek 2009). Multiple dose treatment with poractant alfa reduced both neonatal mortality and pneumothorax in preterm infants with severe RDS (Speer et al. 1992). This study used retreatment criteria based on continued need for mechanical ventilation and oxygen supplementation at 12 and 24 h after the first dose, and about two-thirds of babies needed retreatment. Currently, babies with RDS are being treated with surfactant earlier or even prophylactically, and the need for retreatment is much less than before. Poractant alfa in an initial dose of 200 mg/kg compared to 100 mg/kg leads to reduced need for second and third doses (Halliday et al. 1993; Ramanathan et al. 2004). Although criteria for redosing in the past were fixed, it is best to adopt a more flexible approach (Speer et al. 2013; Sweet et al. 2013). Redosing of infants needing more than 30% oxygen has been compared with more than 40% in a randomized trial using calfactant (Kattwinkel et al. 2000). Babies with uncomplicated RDS did equally well with the higher threshold retreatment criterion, but about one-quarter of those enrolled had complicated RDS (associated with birth asphyxia or sepsis), and they had a lower mortality when retreated earlier (Kattwinkel et al. 2000).

Specific recommendations by surfactant manufacturers differ slightly: for beractant retreatment may be given at intervals of at least 6 h for up to four doses; for poractant alfa treatment may be repeated 12 hourly for two further doses if still intubated and after prophylaxis may be repeated 6–12 h later and after a further 12 h (Speer et al. 2013). However, the Canadian Paediatric Society recommends retreatment of infants needing more than 30% oxygen as early as 2 h after the first dose (Davis et al. 2005), and the European Association of Perinatal Medicine recommends retreatment if there is ongoing RDS indicated by need for mechanical ventilation and supplemental oxygen (Sweet et al. 2013). The latter also recommends that babies extubated to CPAP should be retreated (with the INSURE technique) when they need more than 50% oxygen or if they are likely to need mechanical ventilation (Sweet et al. 2013).

63.4.6 Type of Surfactant

Surfactant preparations studied in the 1990s were either synthetic (containing phospholipids without surfactant proteins) or natural (derived from animal lungs and containing both phospholipids and SP-B and SP-C) (Speer et al. 2013). Of these, the best known synthetic surfactants were colfosceril palmitate and pumactant, but they are no longer available for clinical use. The best known natural surfactants are beractant, calfactant, surfactant TA, and bovactant (all of bovine origin) and poractant alfa (of porcine origin) (Table 2). Recently, other surfactants have been produced in Cuba (Surfacen), Korea (Newfacten), Brazil, and India, but there is little information about them (Speer et al. 2013; Halliday 2006). Also, more recently studied are the so-called new-generation synthetic surfactant preparations (Pfister et al. 2007, 2009) which contain phospholipids and surfactant peptide analogues such as lucinactant (Moya et al. 2005; Sinha et al. 2005) and recombinant SP-C surfactant (Curstedt and Johansson 2006).

As noted earlier, studies comparing synthetic and natural surfactants provide evidence that the latter act more rapidly to improve pulmonary status, and in the longer term they show improved survival with fewer pulmonary air leaks (Ardell et al. 2015). As a result, the older synthetic surfactants, colfosceril palmitate and pumactant, are no longer available as commercial products. There have been 16 trials comparing various natural surfactant preparations (Singh et al. 2015), and the largest of these compared beractant with calfactant for both prevention and treatment of RDS (Bloom and Clark 2005). Unfortunately, the planned sample size was not reached, although more than 2,000 infants had been recruited to the two arms of the study, due to slow recruitment, but in those studied there was no trend to suggest different outcomes including survival without BPD (Bloom and Clark 2005). Studies comparing beractant and poractant alfa are smaller but show that the latter produces a more rapid onset of action in preterm infants with RDS (Ramanathan et al. 2004). This US trial of 293 preterm infants with moderately severe RDS compared two doses of poractant alfa (200 mg/kg and 100 mg/kg) with a 100 mg/kg dose of beractant and found that there was a reduced need for redosing with the higher dose of poractant alfa (Ramanathan et al. 2004). Furthermore, there was improved survival for infants of less than 32 weeks' gestation treated with the 200 mg/kg dose of poractant alfa compared with those treated with beractant. A meta-analysis of nine randomized trials comparing beractant with poractant alfa confirmed an increased mortality prior to discharge with the former (RR 1.44, 95%CI 1.04–2.00; NNH 20, 95%CI 10–100), although the benefit seemed to be limited to those infants treated with the higher dose (200 mg/kg) of poractant alfa (Singh et al. 2015). Despite the numbers of infants studied in these comparisons being modest and the American Academy of Pediatrics stating that it is still "unclear whether significant differences in clinical outcomes exist among the available animal-derived surfactant products" (Polin et al. 2014), poractant alfa is now the most widely used surfactant preparation worldwide (Curstedt et al. 2015).

63.4.7 Concomitant Interventions

Prenatal steroids, methods of respiratory support including CPAP, and caffeine treatment will be considered in this section. There have been at least 21 randomized trials of prenatal steroids involving over 4,000 infants at risk of RDS (Roberts and Dalziel 2006). Treatment with prenatal steroids is associated with an overall reduction in neonatal mortality (RR 0.69, 95%CI 0.58–0.81), RDS (RR 0.66, 95%CI 0.59–0.73), intraventricular hemorrhage (RR 0.54, 95%CI 0.43–0.69), necrotizing enterocolitis (RR 0.46, 95%CI 0.29–0.74), respiratory support and intensive care admissions (RR 0.80, 95%CI 0.65–0.99), and systemic infections in the first 48 h of life (RR 0.96, 95%CI 0.38–0.85) (Roberts and Dalziel 2006). As prenatal steroids are also effective in women with premature rupture of membranes and pregnancy-related hypertension, they should be given in most cases where preterm birth is anticipated before 35 weeks' gestation. Furthermore, there is evidence of synergistic effects of prenatal steroids and postnatal surfactant (Jobe et al. 1993), and therefore both are indicated in cases with high risk of RDS.

The combination of early surfactant treatment and CPAP was assessed in many studies (Dani et al. 2004; Sandri et al. 2010; Verder et al. 1999; Morley et al. 2008; Finer et al. 2010) with two studies comparing nasal CPAP with intubation at birth in very preterm infants (Morley et al. 2008; Finer et al. 2010). It is clear that the combination of CPAP and early surfactant administration reduces the need for mechanical ventilation particularly in infants of greater than 27 weeks' gestation (Bohlin et al. 2008; Sandri et al. 2010; Verder et al. 1999) although the reduction in BPD is rather modest (Bohlin et al. 2008). CPAP started in the delivery room without prophylactic surfactant in infants of 25–28 weeks' gestation does not significantly reduce the rate of death or BPD compared to intubation and is associated with a threefold increased risk of pneumothorax (Morley et al. 2008). However, prophylactic surfactant is not superior to CPAP and early selective surfactant in infants of

25–28 weeks' gestation (Sandri et al. 2010). To facilitate extubation after early surfactant administration by the INSURE technique, the use of respiratory stimulants such as caffeine has been recommended (Bohlin et al. 2008).

There are other reasons for recommending caffeine administration for treatment of apnea of prematurity as this has been shown to reduce risks of BPD, persistent ductus arteriosus (PDA), and need for ductus ligation (Schmidt et al. 2006). The reduced incidence of BPD in infants less than 1,250 g may be due to shortening the duration of mechanical ventilation by about 1 week, and at 18–20 months the surviving caffeine-treated infants had better neurodevelopmental outcomes with less cerebral palsy (Schmidt et al. 2007). Follow-up studies at 5 years of age suggest that these improved neurodevelopmental outcomes may be limited to a reduction in developmental coordination disorder (Doyle et al. 2014). There are clear benefits from treatment of very preterm infants with caffeine for apnea of prematurity and to facilitate extubation following surfactant therapy. There is no clear evidence that early inhaled nitric oxide will prevent BPD in these very immature babies.

Management of PDA in surfactant-treated infants is discussed below with treatment of pulmonary hemorrhage. It is good practice to monitor surfactant-treated infants for PDA and to use prostaglandin synthetase inhibitors (indomethacin or ibuprofen) early to prevent relapse of respiratory status and/or pulmonary hemorrhage.

63.4.8 Other Indications for Surfactant Therapy

Secondary surfactant dysfunction may occur in neonatal respiratory disorders other than RDS where the deficiency is primary. Surfactant inactivation and secondary dysfunction probably occur in meconium aspiration syndrome, congenital pneumonia, pulmonary hemorrhage, acute lung injury or acute respiratory distress syndrome (ARDS), and early stages of BPD (Polin et al. 2014; Robertson and Halliday 1998). There are varying degrees of evidence of effectiveness of surfactant replacement therapy in these conditions, and the evidence base is much weaker than for RDS (Speer et al. 2013; Polin et al. 2014). Four randomized trials (326 infants) of surfactant treatment in meconium aspiration syndrome are included in a systematic review that found improved oxygenation and a reduced need for extracorporeal membrane oxygenation (ECMO) in treated infants (RR 0.64, 95%CI 0.46–0.91; NNT 6, 95%CI 3–25) (El Shahed et al. 2014). However, there were no differences in risk of pneumothorax, CLD, or mortality (RR 0.98, 95%CI 0.41–2.39). These studies used a six-hourly dosing regimen with up to 150 mg/kg of bovine surfactant for up to four doses, and in general the improvement in oxygenation was not seen until after the third dose of surfactant (El Shahed et al. 2014). More recently dilute surfactant lavage has been used to try to remove meconium particles from the lungs (Dargaville et al. 2008), and studies have shown a reduced composite outcome of death or need for ECMO (RR 0.33, 95%CI 0.11–0.96; NNT 5, 95%CI 3–33), but further controlled clinical trials are needed to confirm treatment effect, refine the method of lavage, and compare this technique with standard bolus dosing (Hahn et al. 2013; Choi et al. 2012).

Surfactant inactivation is also present in neonatal pneumonia, and a subgroup of term infants with this condition showed improved oxygenation and reduced need for ECMO in a small, randomized trial of beractant (Lotze et al. 1998). A larger observational study of poractant alfa in infants with group B streptococcal pneumonia showed similar short-term improvements in oxygenation, but these were less impressive than those in preterm infants with RDS (Herting et al. 2000). Although the number of infants with pneumonia and respiratory failure treated with surfactant is relatively small, improved oxygenation warrants further study and continued use of surfactant for this indication.

Pulmonary hemorrhage is now relatively uncommon but may still occur in very preterm infants following surfactant therapy, and it has been postulated that this is due to rapidly improving pulmonary vascular resistance and large left-to-right shunt through a PDA (Halliday and Speer 1995). It is

advisable to monitor preterm infants after surfactant therapy for PDA clinically, echographically, and by blood pressure assessment and to use either indomethacin or ibuprofen at an early stage to prevent pulmonary hemorrhage. Surfactant has been used to treat massive pulmonary hemorrhage and the rationale is that blood inhibits surfactant function. There is evidence of modest improvement in oxygenation after surfactant treatment, but this comes from observational studies rather than randomized trials, which clearly would be difficult to perform (Aziz and Ohlsson 2012). A small randomized trial comparing poractant alfa and beractant to treat preterm infants with pulmonary hemorrhage showed improvements in oxygenation index with both surfactants but no differences in BPD or mortality (Bozdag et al. 2015).

In acute lung injury or ARDS, surfactant is inactivated by proteins and other substances leaking into the alveolar spaces. Pneumonia and sepsis are frequently underlying causes, and surfactant is at least partially effective in reversing signs of respiratory failure in these term infants (Robertson and Halliday 1998; Lotze et al. 1998; Herting et al. 2000). In some preterm infants born to mothers with severe preeclampsia, there may be delayed onset of respiratory distress which could be due to surfactant inactivation, a form of ARDS, and in these infants surfactant may be only partly effective with multiple doses being needed. Acute lung injury may be a prelude to the development of BPD, and surfactant has been used to treat infants with early CLD in a small observational study, which showed transient improvement in oxygenation (Pandit et al. 1995). Late booster doses of calfactant given to preterm infants still ventilated at 7–10 days transiently improved the respiratory severity score without long-term benefits (Merrill et al. 2011). In a large ($n = 511$) randomized trial, similar infants were treated with inhaled nitric oxide and either calfactant or sham instillation every 1–3 days to a maximum of five doses (Ballard et al. 2016). The primary endpoint, survival without BPD, was almost identical in both groups. Recently beractant has been used as a vehicle to deliver budesonide to the airways of preterm infants with severe RDS with a view to preventing BPD (Yeh et al. 2008). In this relatively small randomized trial, there was an unexpectedly large reduction in the combined outcome of death and BPD in infants treated with beractant plus budesonide compared to those treated with beractant alone (32% versus 61%; $p = 0.003$) (Yeh et al. 2008). Recently a larger trial ($n = 265$) of this approach to preventing BPD reported a reduction of the composite outcome, BPD or death, from 66% to 42% ($p < 0.001$; RR 0.58, 95%CI 0.44–0.77; NNT 4, 95%CI 3–8) (Yeh et al. 2016).

Congenital diaphragmatic hernia is also associated with surfactant insufficiency (Cogo et al. 2013), but surfactant treatment in a large series of infants did not improve outcomes (Polin et al. 2014). On the contrary, there were increased rates of CLD, mortality, and need for ECMO in surfactant-treated infants (Keiser and Bhandari 2016). Until more evidence is forthcoming, surfactant replacement cannot be recommended for infants with congenital diaphragmatic hernia although a recent survey found that 45% of pediatric surgeons administer surfactant (Zani et al. 2016).

63.5 Future Developments

Further research is needed to more precisely determine if there any infants who benefit more from prophylactic surfactant as opposed to early selective treatment after CPAP failure. Efforts should continue to reduce rates of BPD while maximizing survival, and this will mean limiting the duration of mechanical ventilation with judicious use of CPAP and perhaps caffeine. There will be further studies aimed to widen indications for surfactant use beyond RDS (Speer et al. 2013; Keiser and Bhandari 2016). Alternative means of administering surfactant without the need for endotracheal intubation will be pursued and tested in large randomized trials. LISA is showing promise but needs special expertise, whereas aerosolization, if perfected and shown to be efficacious, should be easier to administer (Speer et al. 2013). New-generation synthetic surfactants are likely to eventually replace natural surfactants especially if they can be produced more cheaply and in greater quantities (Speer et al. 2013; Polin et al. 2014). In

particular it is likely that surfactants will be used in the future to deliver other drugs, such as budesonide (Yeh et al. 2008, 2016) or other anti-inflammatory agents, directly to the airways to ameliorate acute lung injury and prevent BPD.

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