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REVIEW

What's new in surfactant?

A clinical view on recent developments in neonatology and paediatrics

Jasper V. Been · Luc J. I. Zimmermann

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Abstract Surfactant therapy has significantly changed clinical practice in neonatology over the last 25 years. Recent trials in infants with respiratory distress syndrome (RDS) have not shown superiority of any natural surfactant over another. Advancements in the development of synthetic surfactants are promising, yet to date none has been shown to be superior to natural preparations. Ideally, surfactant would be administered without requiring mechanical ventilation. An increasing number of studies investigate the roles of alternative modes of administration and the use of nasal continuous positive airway pressure to minimise the need for mechanical ventilation. Whether children with other lung diseases benefit from surfactant therapy is less clear. Evidence suggests that infants with meconium aspiration syndrome and children with acute lung injury/acute respiratory distress syndrome may benefit, while no positive effect of surfactant is seen in infants with congenital diaphragmatic hernia. However, more research is needed to establish potential beneficial effects of surfactant administration in children with lung diseases other than RDS. Furthermore, genetic disorders of surfactant metabolism have recently been linked to respiratory diseases of formerly unknown origin. It is important to consider these disorders in the differential diagnosis of unexplained respiratory distress although no established treatment is yet available besides lung transplantation for the most severe cases. *Conclusion*: Research around surfactant is evolving and recent developments include further evolution of synthetic surfactants, evaluation of surfactant as a therapeutic option in lung diseases other than RDS and the discovery of genetic disorders of surfactant metabolism. Ongoing research is essential to continue to improve therapeutic prospects for children with serious respiratory disease involving disturbances in surfactant.

Keywords Surfactant · Lung disease · Respiratory distress syndrome · Preterm · Therapy

Abbreviations

ABCA3	ATP-binding cassette transporter A3
ALI	acute lung injury
ARDS	acute respiratory distress syndrome
bLES	bovine lipid extract surfactant
BPD	bronchopulmonary dysplasia
CHD	congenital diaphragmatic hernia
CLD	chronic lung disease
ECMO	extracorporeal membrane oxygenation
MAS	meconium aspiration syndrome
nCPAP	nasal continuous positive airway pressure
RCT	randomised controlled trial
RDS	respiratory distress syndrome
rSP	recombinant surfactant protein
RSV	respiratory syncytial virus
SP	surfactant protein

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J. V. Been (✉) · L. J. I. Zimmermann
Department of Paediatrics,
Research Institute Growth and Development,
Maastricht University Hospital,
Maastricht, The Netherlands
e-mail: jbee@paed.azm.nl

Introduction

Surfactant is a complex mixture of lipids (90%) and proteins (10%) lining the epithelial surface of the lung. Four surfactant apoproteins have been described: the

hydrophobic surfactant protein B (SP-B) and SP-C and the hydrophilic SP-A and SP-D. Surfactant is synthesised by alveolar type II cells, stored in lamellar bodies that are exocytosed and taken up into the monolayer lining the alveolar epithelium. Traditionally, surfactant is recognised for its surface tension-lowering properties, by which alveolar collapse is prevented and gas exchange is facilitated. More recently, surfactant has been shown to have an important additional role in innate defence of the lung. Key players in this role are SP-A and D, members of the collectin family of proteins. Among their functions are binding, opsonisation and clearance of microbes from the lung and regulation of immune cell activity. Several reviews have addressed their role in detail [80, 148]. Evidence is now accumulating that SP-B, SP-C and the surfactant lipids may be involved in modulation of pulmonary inflammation as well [21, 30, 44, 71, 101, 117].

The relevance of surfactant for pulmonary physiology is highlighted by the respiratory distress syndrome (RDS) seen in preterm infants, caused by an absolute deficiency of surfactant. Affected infants experience respiratory insufficiency often requiring mechanical ventilation. The introduction of exogenous surfactant administration for these infants is generally regarded as one of the most important advancements in the field of neonatology, having significantly decreased neonatal mortality over the last 25 years. Nowadays, the potential benefit of surfactant therapy is evaluated in a wide range of respiratory disorders in both neonates and paediatric patients. Moreover, several disease entities of formerly unknown origin have recently been linked to genetic disorders of surfactant metabolism.

The purpose of this review is to give an overview of these and other recent developments in the field of surfactant, focusing on clinically relevant issues in neonatology and paediatrics.

Surfactant in RDS

In 1959 Avery and Mead established the relationship between surfactant deficiency and RDS seen in preterm infants [9]. Twenty years later, exogenous surfactant was successfully administered to preterm infants with RDS and shown to dramatically improve oxygenation in these babies [51]. In subsequent clinical trials, reductions in neonatal mortality and incidence of pneumothorax were found after surfactant administration [1]. Further trials found that early treatment is superior to late treatment [151], multiple doses are better than a single dose [122] and prophylactic surfactant is associated with better outcome than is rescue treatment [125]. Excellent reviews on the history of surfactant are available [57, 107].

In recent years knowledge of the in vivo surfactant metabolism in RDS patients has increased as a result of metabolic studies. Preterm infants were shown to have a decreased surfactant pool size with decreased synthesis but increased recycling of surfactant when compared to term infants [152]. Furthermore, it was found that both prenatal steroids and exogenous surfactant administration after birth stimulate endogenous surfactant synthesis [25, 26].

Recent developments in surfactant treatment for RDS include new comparative trials of natural surfactants, exploration of alternative modes of administration and evaluation of the use of nasal continuous positive airway pressure (nCPAP) either to decrease the need for surfactant or as an adjuvant therapy following surfactant administration. Moreover, much effort is put into the development of synthetic surfactants for treatment of respiratory distress. This topic is discussed separately.

Natural surfactant

In recent years, several clinical trials have compared the efficacy of different natural surfactants in the treatment of RDS. Natural surfactants are generally derived from either lung lavage or minced lung of bovine or porcine origin.

Four studies have compared beractant (Survanta) and poractant-α (Curosurf) [12, 93, 112, 126]. Curosurf was found to have a more rapid onset of action in most studies [93, 112, 126]. A meta-analysis of these studies plus one unpublished study suggested a significant decrease in neonatal mortality after Curosurf treatment [57]. However, three of these studies have compared a Curosurf dose of 200 mg/kg with a Survanta dose of 100 mg/kg [93, 112, 126]. When these studies were excluded from analysis, the difference in mortality after treatment with comparable doses of both surfactants was not statistically significant [57]. Malloy and colleagues reported a significant decrease in the incidence of persistent ductus arteriosus after Curosurf treatment [93]. None of the other studies found such an effect and it is unclear whether this difference may be explained by the dosing difference as well.

Baroutis and colleagues compared the effects of three different surfactant preparations: Curosurf, Survanta and Alveofact [12]. Treatment with either Curosurf or Alveofact was associated with a decrease in days on the ventilator, days on oxygen and hospital stay, but no significant improvement in morbidity and mortality. A more recent study comparing Survanta and Alveofact reported a decrease in chronic lung disease (CLD) with Survanta [59]. However, CLD was defined as oxygen need at 28 days of age, a definition that does not take into account the gestational age of the infant and is generally regarded to be imprecise and outdated. There was a decrease in days on the ventilator, days on oxygen and length of hospital stay

with Survanta. The need for postnatal steroids was decreased in the Survanta group as well; however, their overall use was very high compared to current standards.

Two studies have compared Survanta and Infasurf (calfactant) for the treatment of RDS [7, 17]. The largest study compared the efficacy of the two surfactants for prophylactic administration as well as for rescue treatment [17]. Infasurf was found to have a more rapid effect, without having an effect on overall incidence of bronchopulmonary dysplasia (BPD) or mortality. Subgroup analysis showed a decrease in mortality after prophylactic Survanta treatment in infants under 600 g. A more recent, smaller study reported a decrease in number of doses required with Infasurf without any differences in outcome [7].

One small comparative trial was reported on bovine lipid extract surfactant (bLES) and Survanta [86]. Treatment with bLES was associated with a more rapid improvement in oxygenation, yet no effect on short-term outcome was seen.

In summary, most differences in effectiveness between natural surfactant preparations are short-lived. On the basis of currently available evidence, no preparation can clearly be considered superior to another with regard to morbidity and mortality. More data would be needed and future studies should include comparison of long-term outcome parameters. However, the clinical relevance of these differences is likely to be minimal; therefore, future studies should focus on more relevant aspects of surfactant therapy.

Timing of surfactant

Many studies have investigated the ideal timing of surfactant administration. Systematic reviews of earlier studies have found a decrease in the incidence of pneumothorax, pulmonary interstitial emphysema, CLD and mortality with early (within 2 h after birth) versus delayed surfactant administration [151] and a decrease in pneumothorax and mortality with prophylactic surfactant administration versus selective rescue therapy [125].

As stressed by Horbar and colleagues, these trials were conducted at a time when the use of antenatal steroid administration was much lower than it is today. Therefore, the observed difference between early and delayed surfactant therapy may be smaller in current practice [69]. A more recent trial still suggests a positive effect of early surfactant administration in intubated infants, albeit without any effect on morbidity and mortality [88].

Surfactant and nCPAP

An important issue is the use of nCPAP, either to prevent intubation and surfactant administration or to accelerate extubation after surfactant is given. A recent Cochrane review showed that intubation and early administration of surfactant followed by extubation to nCPAP was associated with decreased ventilator requirement, but an increase in number of surfactant administrations when compared to selective surfactant and continued ventilation [129]. No difference in BPD incidence was detected. Dani and colleagues later showed that, when intubated and given surfactant, infants may benefit from early extubation to nCPAP [40]. Whether intubation for the purpose of surfactant administration is favourable for larger preterms with mild to moderate RDS is questioned by a recent study showing an increase in median duration of ventilation with elective intubation and surfactant [46].

The potential of the initial use of nCPAP to prevent intubation and administration of surfactant is the subject of current studies. Potential side effects of intubation and high costs of surfactant administration might thus be avoided. Retrospective studies suggest that, when compared to early initiation of mechanical ventilation, early nCPAP decreases the incidence of intraventricular haemorrhage and improves survival but may increase the risk for necrotising enterocolitis when nCPAP fails [2, 5]. However, only part of the infants on early mechanical ventilation received surfactant. More recent data from Te Pas and colleagues suggest that even if early nCPAP fails, it may still result in a decreased BPD risk when compared to infants intubated in the delivery room [133].

Ideally, avoidance of intubation and subsequent mechanical ventilation would involve early initiation of nCPAP in combination with an alternative mode of surfactant administration. The combined use of early nCPAP and surfactant administration through a thin endotracheal catheter was reported to decrease the need for mechanical ventilation in very low birth weight infants [83]. Other potential alternatives for endotracheal administration include aerosolisation [48], bronchoscopic administration [14], nasopharyngeal deposition [77] and administration of surfactant via a laryngeal mask [22, 136]. Clearly, controlled trials are needed to evaluate the safety of alternative modes of surfactant administration and the potential of a combined approach with early nCPAP to decrease the subsequent need for mechanical ventilation and improve outcome.

Synthetic surfactant

A major disadvantage of commercially available natural surfactants is their price. Therefore much effort has been put into development of synthetic surfactants. The basis of these preparations is a highly simplified phospholipid mixture. The lack of surfactant proteins is a disadvantage compared to natural surfactants. Natural surfactant preparations contain variable amounts of SP-B and SP-C that enhance surface tension-lowering properties and long favoured their use above synthetic preparations [123]. The

potential of several additives with surfactant protein-like properties to increase the efficacy of synthetic surfactant preparations is currently under evaluation.

Two synthetic surfactants containing such additives have been tested in clinical trials. One is Venticute, which contains recombinant SP-C (rSP-C). However, no trials involving Venticute in preterms with RDS have yet been published. The other, lucinactant (Surfaxin), is characterised by the addition of KL4 (sinapultide), a non-natural polypeptide that was designed to resemble SP-B [38]. Two trials comparing prophylactic use of Surfaxin to a natural surfactant in the treatment of RDS showed no differences in relevant outcome parameters [99, 121]. However, these trials were designed to show only 'noninferiority', and the study comparing three surfactant preparations was underpowered to detect a difference between Surfaxin and the natural surfactant Survanta [76].

So although synthetic surfactants, especially those with surfactant protein-like additives, have theoretical advantages over natural surfactants, to date none has been shown to be superior to natural preparations in comparative trials [38]. Yet the search for new synthetic surfactant protein analogues goes on. Recent data from in vitro and animal studies are promising regarding efficacy of different SP-B peptides, modified rSP-C with improved function and polymyxin B as possible future additives to synthetic surfactants [38]. Moreover, a group of additives capable of decreasing surfactant inactivation is under investigation, showing promising results. These include chitosan [153], hyaluronan [91, 92, 141], dextran [108] and polymyxin B [27, 130]. The potential of these additives lies in their use in RDS and meconium aspiration syndrome (MAS), where inactivation of surfactant by albumin and meconium respectively decreases its efficiency.

Surfactant in other neonatal lung disease

Congenital diaphragmatic hernia (CDH)

CDH is a serious disease associated with a mortality of 25–74%, primarily due to respiratory insufficiency [43]. Surfactant deficiency and dysfunction have been found in a lamb CDH model and respiratory failure in these animals improved after exogenous surfactant administration [143]. Data on surfactant pool size and function in infants with CDH are inconclusive [33, 35, 74, 85]. Only one small, randomised trial of surfactant in CDH patients on extracorporeal membrane oxygenation (ECMO) is available, showing no benefit [89]. Incidental reports do suggest a beneficial effect [10, 18, 53]. Recently, the CDH study group has retrospectively compared the outcomes of CDH infants that did and did not receive exogenous surfactant during admission. No difference was observed in term infants [137], while surfactant administration was associated with increased mortality in preterms [85]. However, this difference was not statistically significant after adjusting for gestational age and Apgar score. When only infants on ECMO were considered, surfactant still did not improve survival [36].

In conclusion, although surfactant therapy is incorporated in CDH treatment protocols in many centres, this strategy is not supported by evidence and is advised to be used only in the context of a randomised trial [43, 100].

Meconium aspiration syndrome (MAS)

Perinatal meconium aspiration affects surfactant function and metabolism in several ways. Meconium has an extremely high surface tension [116], inhibits surfactant function [11, 66, 98, 132] and causes pneumonitis with direct toxicity to alveolar type II cells [68, 109]. Furthermore, we have recently found decreased alveolar surfactant content and synthesis in infants with MAS [73].

Possible treatment options for MAS involving surfactant include bolus surfactant administration and lung lavage using either saline or diluted surfactant. Initial case series reported temporary improvements in oxygenation and a decreased need for ECMO after bolus surfactant treatment [8, 79]. Two randomised trials of bolus surfactant therapy have been published [47, 90]. A meta-analysis of these studies showed a decreased need for ECMO in surfactant-treated infants without any relevant improvement in outcome [124]. An important difference between the two studies was the timing of surfactant administration. With early treatment (within 6 h after birth), Findlay and colleagues did report additional beneficial effects, such as decreased air leaks and shorter duration of ventilation [47]. Based on current evidence, Dargaville and Mills advocate early administration of a surfactant known to resist meconium inactivation in severely affected infants, with repeated doses when needed [41].

Meconium can be effectively removed from the lung by lavage [87]. Most studies report a subsequent improvement in oxygenation above pre-lavage baseline, with earlier extubation and a decrease in pneumothorax incidence [41]. Two randomised controlled trials (RCT) of lavage therapy in MAS have been reported. Only limited data are available from one study, suggesting that surfactant lavage is better than saline lavage [110]. No significant differences were found between infants lavaged with Surfaxin and non-lavaged infants in the other trial [147]. However, additional studies are underway [41]. Further trials should focus on the comparison between bolus surfactant therapy and surfactant lavage.

In conclusion, infants with MAS seem to benefit from surfactant therapy when started early and repeated when

necessary. There is insufficient evidence as yet to support the use of surfactant lavage therapy for MAS outside the setting of a clinical trial [41]. As discussed earlier, the development of synthetic additives capable of decreasing meconium-induced surfactant inhibition may help to increase future efficacy of surfactant therapy for MAS.

Other neonatal lung diseases

Decreases in alveolar surfactant pool size and surfactant recycling have been described in chronically ventilated infants progressing to or suffering from BPD [32, 34, 127]. Therefore, surfactant might be beneficial in treating these infants. Indeed, incidental reports suggest short-term improvement after surfactant administration in chronically ventilated preterms, urging the need for further studies [15, 78, 96]. Other neonatal pulmonary disorders that may benefit from surfactant therapy include haemorrhagic pulmonary oedema [4] and neonatal pneumonia [64], yet once again only incidental reports addressing these issues are available.

Surfactant in paediatrics

Surfactant has been evaluated as a potential intervention in respiratory diseases beyond the neonatal period. Several reports have focused on the use of surfactant in acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). In paediatric ARDS/ALI patients, acute improvement of oxygenation is seen with surfactant administration [65, 94, 97, 144–146]. No additional effects on outcome were noted in the first RCT [97]. In a more recent RCT in ventilated children with respiratory failure and bilateral radiographic abnormalities, treatment with Infasurf was associated with a decrease in mortality [145]. The mortality effect was greatest in the subgroup of infants (age <1 year), yet overall mortality was not significantly different after adjustment for immunocompromised status. Concerns about the study being underpowered and the increased incidence of hypotension and transient hypoxaemia in the treatment group warrant further evaluation before surfactant administration can be routinely recommended in paediatric ARDS/ALI [39]. An important determinant of surfactant response seems to be the nature of the lung injury causing the respiratory failure. Patients with direct lung injury may benefit more than do patients with indirect lung injury [145]. Future studies should address differences in ALI aetiology in the patients studied.

Several studies have investigated a possible role for surfactant in treatment of bronchiolitis. A recent systematic review evaluating three trials reported a significant decrease in duration of ventilation and of hospital admission with surfactant therapy [138]. However, it is generally felt that current evidence is insufficient to establish the role of surfactant suppletion in bronchiolitis and that additional trials are needed [42, 81, 138].

Surfactant disturbances have been described in a wider range of paediatric lung diseases and recent case series suggest a potential beneficial role for surfactant in the treatment of lobar atelectasis [82], intrapulmonary haemorrhage [55], *Pneumocystis carinii* pneumonia [37] and as an adjuvant therapy in ECMO patients [63]. Clearly, additional studies are needed to establish the safety and potential benefit of surfactant therapy in these disorders as well.

Genetic disorders of surfactant

SP-B deficiency

In recent years, several genetic disorders affecting surfactant metabolism have been identified. SP-B deficiency, first described in 1993 [104], is the most serious of these. It is a rare autosomal recessively inherited disease, in the majority of patients caused by the 121ins2 mutation [105]. SP-B is critical for lowering alveolar surface tension. Adding to the surfactant dysfunction caused by the deficiency of SP-B is the associated incomplete processing of SP-C [139]. In almost all cases a total absence of SP-B is present, which is invariably lethal [60]. Babies present with respiratory failure shortly after birth, only partially and transiently being responsive to exogenous surfactant administration. To date, the only therapeutic option for these patients is lung transplantation, which should be performed within weeks to months [61]. Recently, Palomar and colleagues reported that the outcome for lung transplantation in SP-B-deficient patients is comparable to patients transplanted for other reasons [111]. However, Hamvas reports that approximately half the families of children eligible for lung transplantation decline and another 30% of patients die awaiting transplantation [60].

SP-C-associated disease

In recent years, several mutations in the SP-C gene have been identified and connected to respiratory disease. The incidence of SP-C-associated disease appears to be considerably higher than that of SP-B deficiency [60]. This is partly due to the fact that SP-C mutations are inherited in a dominant manner [60]. On the other hand, approximately half of the disease-associated mutations are spontaneous mutations [60]. The most common mutation I73T, as well as most other mutations, results in production of misfolded SP-C that accumulates within the alveolar type II cell [13, 75, 140].

The presentation and characteristics of respiratory diseases resulting from SP-C mutations are diverse and unpredictable [60]. Patients carrying mutations may present anywhere between the newborn period and adulthood. In a large cohort of term newborns with unexplained respiratory disease, the incidence of SP-C gene mutations was shown to approach 10% [142]. Asymptomatic patients carrying SP-C mutations have also been identified [28, 134]. Newborns may present with RDS-like symptoms despite term birth. In paediatric patients interstitial lung disease may present with gradual onset of respiratory insufficiency, hypoxaemia and failure to thrive. Some patients remain stable or even improve, while others progress to respiratory insufficiency, eventually requiring lung transplantation.

No standard treatment for SP-C-associated disease is available. Some authors have seen clinical improvement after treatment with hydroxychloroquine [3, 114] or repeated lung lavage along with administration of corticosteroids and azathioprine [135], while others have not [19, 31]. Clearly, additional studies are needed to further investigate possible treatment options for SP-C-associated disease.

ABCA3-associated disease

The most recently discovered genetic disruption of surfactant metabolism is caused by mutations in the gene encoding for ABCA3 [119]. ABCA3 is an ATP-binding cassette (ABC) protein localised at the limiting membrane of lamellar bodies [102, 149]. In vitro studies show that depending on the mutation present, the mutant ABCA3 protein is either retained at the endoplasmic reticulum or is appropriately localised yet exhibits a decreased capacity to hydrolyse ATP [95]. The exact role of ABCA3 is unknown; however, other members of the ABCA protein family are involved in lipid transport [128]. A specific role for ABCA3 in lipid metabolism is further supported by the detection of reduced lung levels of phosphatidylglycerol and phosphatidylcholine subtypes in ABCA3 knockout mice, while levels of other phospholipids and cholesterol were unaffected [49]. Along with other studies, this work further suggests a key role for ABCA3 in lamellar body formation [29, 49, 103]. Abnormal lamellar body formation, surfactant deficiency and surfactant dysfunction have indeed been found in patients carrying ABCA3 mutations [20, 23, 52, 119].

Most patients with ABCA3 mutations described thus far presented in the neonatal period with progressive respiratory distress, often being lethal. Hydroxychloroquine and corticosteroids have been used in the management of ABCA3-associated disease, yet their efficiency in treating the disorder is unclear [23]. For these patients, lung transplantation is currently the only treatment option [24, 52]. However, Bullard and colleagues have recently stressed the fact that most patients described thus far were derived from highly selected populations of infants with unexplained severe respiratory distress [23]. The same group has identified ABCA3 mutations in paediatric patients with interstitial lung disease, suggesting that defects in ABCA3 may be involved in a greater range of respiratory diseases [24]. Research on ABCA3-associated respiratory disease is clearly evolving and knowledge about the disorder will increase in the near future.

We wish to underline the importance of considering genetic disorders of surfactant metabolism in the differential diagnosis of both unexplained respiratory failure and interstitial lung disease in the newborn period and beyond. When such a disorder is suspected in a patient, one should turn to a specialised laboratory for establishment of the diagnosis.

Surfactant protein polymorphisms and lung disease

In addition to the mutations described above, more common polymorphisms in surfactant proteins have been linked to both increased and decreased risks of developing neonatal and paediatric pulmonary disease. Genetic variants of the SP-B gene have been linked to increased risks for both respiratory distress [50, 62] and BPD [115]. Common SP-A alleles, in interaction with the SP-B Ile131Thr genotype, have been associated with RDS susceptibility, while others seem to decrease RDS risk [56, 58]. Recently, polymorphisms in SP-C genes have also been linked to RDS [84]. The susceptibility for respiratory syncytial virus (RSV) infection is altered by polymorphisms of SP-A and SP-D, known modulators of innate immunity. In addition, associations of surfactant protein polymorphisms with extrapulmonary diseases exist, such as recurrent ear infections [113] and meningococcal disease [72].

The relevance of these associations between surfactant protein haplotypes and neonatal and paediatric pulmonary and infectious diseases remains unclear. Associations may differ between populations, hence the finding of contrasting risk associations between SP-B polymorphisms and RDS [62]. Larger studies are clearly needed to confirm current findings. Possible future applications include individual risk determination and subsequent surfactant protein administration.

Future directions and conclusion

As highlighted in this review, substantial progression has been made in recent years considering the role of surfactant therapy in neonatal and paediatric lung diseases. However, many questions remain unanswered. Efforts should be made to investigate the roles of nCPAP and alternative administration routes for surfactant in the treatment of preterm infants. Further development of synthetic surfac-

tants to enhance their surface tension-lowering properties and capacity to withstand inactivation may increase future efficacy of surfactant therapy. More ideally, one should be able to stimulate endogenous surfactant synthesis in preterm infants, preferably antenatally. A potential candidate drug would be docosahexaenoic acid, which has been shown to stimulate synthesis of dipalmitoyl phosphatidylcholine, the major phospholipid in surfactant, in preterm mice when administered to the mother during pregnancy [16]. Another promising future application for surfactant is its use as a carrier for drug administration directly into the lung. In this way drugs are allowed to act locally with minimisation of unwanted systemic effects. Possible candidate drugs include immunosuppressants [54], vasodilators [106] and β-sympathicomimetics [150]. Investigational drugs that have been administered in animal models using surfactant as a carrier include a 5-lipoxygenase inhibitor [6] and recombinant human Clara cell secretory protein (rhCC10) [118]. Both agents have been shown to decrease experimental lung injury in these models. The anti-inflammatory and antimicrobial characteristics of SP-A and SP-D make them attractive potential therapeutic agents as well. Administration of recombinant SP-D fragments in animal models results in enhanced pulmonary clearance of RSV [67], a reduced allergic response [45, 120, 131] and prevention of endotoxin shock [70]. However, SP-A and SP-D are very large and complex molecules, making construction of functional recombinant whole proteins extremely difficult if not impossible. Much more research is needed to evaluate a possible role for surfactant proteins in the treatment of inflammatory diseases. Furthermore, the general evolution of gene therapy involves potential applications in the genetic disorders of surfactant metabolism, primarily SP-B deficiency.

More than 25 years after the introduction of exogenous surfactant therapy, research around surfactant is still evolving. Surfactant remains a hallmark in the treatment of RDS, especially in very preterm infants. Future research should focus on potential ways to avoid intubation and mechanical ventilation and give surfactant via an alternative route. The therapeutic role of surfactant in other neonatal and paediatric lung diseases is less clear and needs further evaluation. Finally, genetic disorders of surfactant metabolism should be taken into account in the differential diagnosis of respiratory distress and interstitial lung disease in children.

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