Surfactant therapy in 2011

Surfactant therapy has revolutionised neonatal respiratory care since its introduction in the 1980s and is now recommended routinely early in the course of respiratory distress syndrome. Recent guidelines have attempted to achieve a balance between the role of surfactant therapy, which requires at least a short period of mechanical ventilation, and a more conservative approach using continuous positive airway pressure alone. In this review current recommendations for optimising the use of surfactant are described.

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Key points

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1. Surfactant therapy plays an important role in the management of babies with RDS.
2. If surfactant therapy is needed then the earlier it is given the better, including prophylaxis for some very high risk babies.
3. If babies with RDS can be managed with CPAP alone then surfactant may not be needed.
4. Surfactant can also be used in babies on CPAP without resorting to prolonged mechanical ventilation.
5. More than one dose may be needed.

Recent published guidelines from the United States, Canada and Europe outline expert opinion on how surfactant therapy should be used in babies with respiratory distress syndrome (RDS) in the current era[1-3]. The common theme is that surfactant replacement therapy, if it is going to be used, should be used as early as possible and at present natural (animal derived rather than synthetic) surfactants are the treatments of choice. This comes with the caveat that as often as possible we should try and manage babies without resorting to intubation and mechanical ventilation by maximising the use of continuous positive airway pressure (CPAP). A summary of recommendations for surfactant therapy from the 2010 European Guidelines is shown in **TABLE 1**.

Surfactant replacement therapy is one of the most intensively studied interventions in medicine. There are now 185 randomised controlled trials of surfactant therapy in the Cochrane Register of Controlled trials and these have been subjected to 29 Cochrane systematic reviews. Twelve different surfactant preparations have been used in clinical trials[4], with timing of first administration in trials ranging from immediate prophylaxis in the delivery room to intervention when babies are at least six to eight hours old[5], and the number of doses ranging from one to four[6]. Despite all of this evidence, it is still sometimes difficult in individual cases to decide when best to intervene with surfactant, particularly in babies who are apparently managing on CPAP early in the course of RDS. The aim of this review is to summarise where we are now with surfactant therapy, and the reasoning behind some of the 2010 European recommendations.

Which surfactant is best?

There are several different types of surfactant preparation licensed for use in babies with RDS. These include synthetic

Type of surfactant	Natural better than synthetic
Prophylaxis	Under 26 weeks' gestation, or if needing intubation
Timing of first rescue dose	Develop individual protocols for when to intervene as RDS progresses based on oxygen requirements and gestational age
Dose	200mg/kg better than 100mg/kg for rescue therapy if using poractant alfa. Otherwise use 100mg/kg
Ventilation vs CPAP	Use CPAP in preference. Extubate to CPAP as early as possible after surfactant. Consider INSURE technique for babies on CPAP who require surfactant
Second and third doses	Give second and occasionally third doses of surfactant if ongoing evidence of RDS such as persistent requirement for mechanical ventilation and supplemental oxygen

TABLE 1 Summary of 2010 European recommendations for surfactant therapy.
Key: *RDS=respiratory distress syndrome; CPAP=continuous positive airway pressure; INSURE=INtubation, SURfactant and Extubation to CPAP .*

(protein-free) surfactants and natural surfactants (derived from animal lungs) and both types of surfactant showed benefit compared with placebo. Natural surfactants contain surfactant proteins which enable them to work more quickly although it was not initially clear if this was an advantage. Direct comparative trials of synthetic versus natural surfactants took place during the 1990s and 11 have been subjected to a Cochrane systematic review, with the meta-analysis showing improved outcomes if natural surfactants are used[7]. Natural surfactants result in fewer pneumothoraces and a reduction in mortality (typical relative risk 0.87, 95% CI 0.76 to 0.98). In the UK, the older synthetic surfactants Exosurf® and Pumactant® are no longer on the market.

In recent years attempts have been made to produce improved synthetic surfactants by the addition of peptides which mimic the actions of natural surfactant proteins. The rationale for doing this is that synthetic surfactants have highly reproducible compositions and can be produced in large quantities; they may reduce potential risk for immune reactions to animal proteins or transmission of infections and may be more acceptable to some cultures on religious grounds. The synthetic surfactant that has been studied the most is lucinactant, a surfactant preparation containing phospholipids and a high concentration of a synthetic peptide (KL4 peptide) that resembles one of the domains of surfactant protein B. Comparative studies confirmed that lucinactant was better than one of the older synthetic surfactants, but not superior to existing natural surfactant preparations and the product has not yet been licensed for use in newborns[8,9].

What dose should be used?

The doses of surfactant we use today come directly from the original surfactant studies from the 1980s, and these doses were usually chosen pragmatically based partly on the volume of surfactant that could be tolerated. The early studies of poractant alfa used 100mg/kg or 200mg/kg (1.25-2.5mL/kg) and for beractant used 100mg/kg (4mL/kg) and these are still the doses used today. Early small dose finding studies suggested better outcomes with higher initial doses of surfactant. In the early 1990s an attempt was made to determine if a higher starting dose (200mg/kg vs 100mg/kg) and maximum allowable cumulative dose (600mg/kg vs 300mg/kg) of poractant alfa would result in improved survival or reduction of bronchopulmonary dysplasia (BPD). Babies treated with 200mg/kg showed a more sustained improvement in oxygenation and fewer of them required a second dose (69% vs 77%). However these early improvements did not appear to influence the primary outcome which was death or oxygen dependency at 28 days (51% each group) and death before discharge (23.5% vs 25 %)[10]. The authors concluded that the lower dose regimen was equally effective as the higher and should be employed as it is more cost effective.

It must be borne in mind that this study was performed in an era when exposure to antenatal steroids was only 17%, the surfactant was given as relatively late rescue therapy and CPAP was not as widely used. Nowadays, in the era of non-invasive respiratory support the issue of whether different surfactant doses can influence management has been re-explored. Pharmacokinetic studies using carbon-13 labelled poractant alfa show that a higher initial dose of surfactant results in a significantly longer half-life[11] and this is mirrored by observed clinical differences, including better oxygenation and less need for subsequent redosing in babies who receive the higher dose[11,12]. The difference is likely to be due to recycling of degraded surfactant components.

Several clinical studies have compared the recommended dose of 200mg/kg poractant alfa with the recommended dose of 100mg/kg of beractant. Individually the studies are small, but the higher dose of surfactant resulted in more rapid improvement in oxygenation. Meta-analysis of combined survival data from 328 babies in these studies suggest a reduction in mortality favouring 200mg/kg of poractant alfa[13].

When should surfactant be given?

The issue of timing of surfactant therapy continues to cause debate. In an ideal world surfactant replacement would only be used for babies with surfactant deficiency who require mechanical ventilation. The difficulty is that the evidence until recently has directed clinicians towards the earliest possible administration of surfactant in order to improve survival, although we know that intubation and ventilation may be harmful and there is no reliable predictive test to determine if an individual baby is at risk of developing severe RDS. The 2010 European Consensus Guideline suggests a policy of selective prophylaxis for some babies at very high risk of RDS, with very early rescue surfactant for the remainder of extremely preterm babies, and avoiding intubation for surfactant in the 'more mature' preterm babies if it is considered likely that CPAP will suffice. However even since this 2010 guideline further important studies have been published which provide additional information to address this question.

It is clear that if surfactant is used for established RDS in *ventilated* babies then it is more effective when given earlier rather than waiting until babies require higher amounts of supplemental oxygen[5]. Similarly prophylactic administration of surfactant has been shown to be superior to rescue therapy. Meta-analysis of eight trials during the 1990s using natural surfactants showed a 39% reduction in neonatal mortality if babies less than 32 weeks are treated within 15 minutes after birth compared with treatment a few hours later[14]. There was also a reduction in pneumothorax and pulmonary interstitial emphysema. However almost 50% more infants received surfactant when being treated prophylactically, suggesting that many of them may not have required surfactant. There was no reduction in BPD in the Cochrane meta-analysis[14], however separate individual patient analysis of the three trials in which poractant alfa was used showed a significant reduction in the risk of oxygen dependency at 28 days of age [adjusted odds ratio 0.54 (95% CI 0.34 to 0.86)][15]. Of the studies included in the Cochrane meta-analysis, the earliest median time of administration in the rescue surfactant group was one and a half hours after birth.

The use of antenatal steroids and CPAP for respiratory support was much lower 20 years ago when these studies were undertaken. Many babies included in these trials would not nowadays be considered eligible for surfactant, particularly if they had received the benefit of antenatal steroids and were managing well on CPAP. There was a strong argument to try and determine which babies really require surfactant prophylaxis if antenatal steroids and CPAP are used. Units adopting policies of more aggressive CPAP use seemed to have reduced rates of BPD with no increase in mortality[16], but it is only very

recently that the question of delivery room surfactant versus early initiation of CPAP has been addressed.

The first of these studies was the COIN trial[17]. In this study 610 babies born between 25 and 28 weeks' gestation who were breathing spontaneously but requiring respiratory support were randomised to initiation of nCPAP (8cm H_2O) or intubation and mechanical ventilation in the delivery suite. Babies in the CPAP arm were not given surfactant unless they required intubation. Surfactant therapy was not mandated in the intubation arm of the trial, with 77% of intubated babies receiving surfactant compared with 38% of those initiated on nCPAP. The primary outcome of death or BPD was not different between groups (34% CPAP group vs 39% intubation group). The early nCPAP group had fewer days of mechanical ventilation (median 3 vs 4 days; p<0.001) but had a higher incidence of pneumothorax (9% vs 3%; p<0.001). This study proved that for a selected population of preterm babies where antenatal steroid use was high (94%) and who were breathing after five minutes that initiation of early CPAP would reduce the need for mechanical ventilation and surfactant therapy without there being any reduction in survival or increase in BPD.

There was still concern that managing preterm babies without early surfactant exposed them to an increased risk of air leak. However as there was no defined protocol for the administration of surfactant, this study did not provide evidence for the superiority of CPAP over early surfactant.

Another important study was CURPAP[18] in which 208 babies of 25 to 28 weeks' gestation were enrolled if they did not need intubation for stabilisation. Within 30 minutes after birth babies were either initiated on nCPAP or intubated for prophylactic surfactant followed by immediate extubation to nCPAP. The number needing subsequent intubation and mechanical ventilation within the first five days of life was similar in both groups. In both groups 78% of babies survived without BPD showing that prophylactic surfactant was not superior to nCPAP and early selective surfactant.

The largest study designed to address this issue was the SUPPORT trial[19]. In this multicentre 2-by-2 factorial study (also designed to assess the benefits of high versus low oxygen saturation targeting) a total of 1,316 babies born between 24 and 27 weeks were randomised to receive either intubation and surfactant within one hour of birth or early initiation of CPAP. There was a very high rate of treatment with antenatal steroids. The intended treatment allocations were largely successful, with surfactant being given 99% of the time in the surfactant group and initiation of CPAP in the delivery room 81% of the time for the CPAP group. Thirty three percent of the CPAP group never received surfactant. The CPAP group had a reduced total number of days of mechanical ventilation (mean 25 vs 28; p=0.03), a reduced incidence of steroid therapy for BPD (7.2% vs 13.2%; p<0.001) but there was no significant difference in the combined outcome of death or BPD at 36 weeks' postmenstrual age (48% vs 51%; p=0.3).

This study offers a strong argument against routine intubation for prophylactic surfactant in extremely preterm babies in the current era of CPAP use. However, one cannot assume that this finding should be generalised to include babies in whom there had been inadequate time for completion of antenatal steroids. Furthermore, it should be noted that both groups of infants in the SUPPORT trial remained on ventilation for a long time (almost four weeks) compared to those treated in Europe or Australia (three or four days) and this cannot be explained entirely on the lower gestational age of the former.

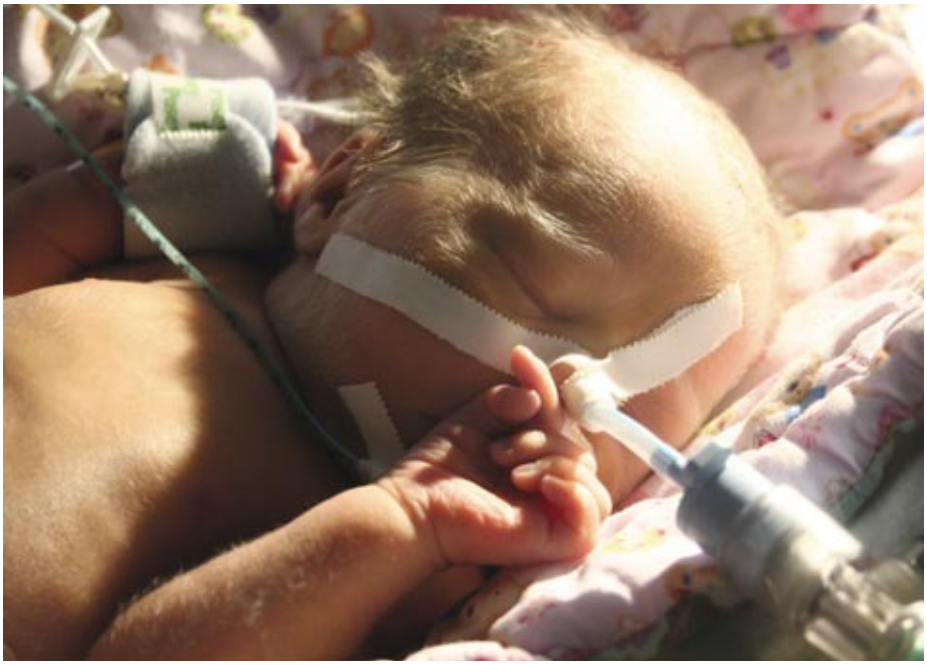

FIGURE 1 A baby on mechanical ventilation.

Surfactant administration, ventilation and CPAP

Traditionally surfactant administration takes place after intubation and at least a short period of mechanical ventilation (**FIGURE 1**) and it is probably these, rather than surfactant *per se* that are potentially harmful. It is now well established that prolonged mechanical ventilation can be avoided in some babies who require surfactant if the INSURE technique is employed (INtubation, SURfactant and Extubation to CPAP). Six studies undertaken during the 1990s and early 2000s compared early surfactant and CPAP with later surfactant and ventilation. Meta-analysis shows that babies with RDS managed with a policy of earlier surfactant followed by extubation to CPAP have less need for mechanical ventilation (RR 0.67 95% CI; 0.57-0.79), fewer pneumothoraces (RR 0.52 95% CI; 0.28-0.96) and less BPD (RR 0.51 95% CI; 0.26-0.99)[20]. It was also demonstrated that the earlier the decision is made to intervene with INSURE the greater the chance of avoiding ventilation[21].

Avoiding intubation altogether has been attempted by various methods[13] but none is in widespread use today. Intra-amniotic instillation of surfactant in the vicinity of the fetal mouth and nose is technically feasible, but the risks of this relatively invasive procedure seem to outweigh the benefits[22]. Nasopharyngeal and laryngeal mask instillation have also been described but more work is needed before these

methods can be recommended. Surfactant nebulisation has also been employed although lipids are relatively difficult to aerosolise, and most of the surfactant gets deposited in the ventilator tubing resulting in the need for very large doses to be used[23]. A small pilot study of aerosolised lucinactant using a vibrating membrane nebuliser has demonstrated the feasibility of this method for surfactant treatment of babies on CPAP but more research is needed before it can be recommended[24]. Another method of surfactant administration while avoiding ventilation has been developed in German neonatal units in recent years. This technique involves placement of a fine intratracheal catheter while babies remain spontaneously breathing on CPAP[25]. In a randomised trial of 220 infants of 26 to 28 weeks' gestation 28% of those given surfactant non-invasively by a fine gastric tube needed mechanical ventilation compared to 45% of those treated with CPAP and rescue surfactant ($p<0.05$). Long-term outcomes were not reported but this may prove to be a promising technique to reduce the need for intubation and mechanical ventilation in surfactant-treated preterm infants[25].

Timing of second and third doses of surfactant?

A number of trials were designed to assess whether repeated doses are more beneficial than a single dose of surfactant. In babies with severe RDS, multiple rather than single doses of poractant alfa were superior in reducing the incidence of mortality and pneumothorax[26]. In a study of more mature babies with RDS, repeat dosing with beractant reduced secondary deterioration in gas exchange[27]. Beyond two doses there does not appear to be much additional benefit from repeat dosing. A higher cumulative dose of phospholipid, 380mg/kg over five doses was not shown to be superior to 242mg/kg over three doses in the Curosurf® 4 trial[10]. A Cochrane review shows that a strategy of allowing multiple doses of natural surfactant rather than a single dose further reduces the risk of pneumothorax (RR 0.51 95% CI 0.30 - 0.88) and there is also a trend towards reduction in mortality[6]. However in these early studies the first dose of surfactant was given comparatively late about 6-12 hours after birth and the policies at the time would have been to use longer periods of mechanical ventilation rather than CPAP.

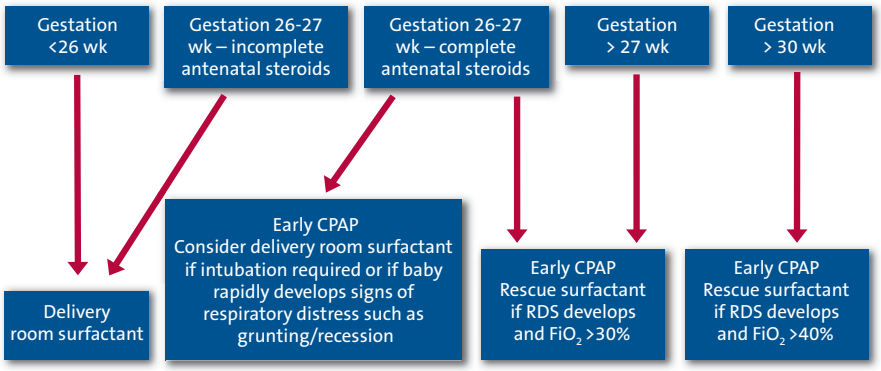

FIGURE 2 Suggested protocol for intervention with surfactant based on European Consensus Guidelines 2010.

Manufacturers of natural surfactants make specific recommendations regarding re-treatment: beractant (Survanta®) – may be repeated within 48 hours at intervals of at least six hours for four doses; poractant alfa (Curosurf®) – 12 hours later for two further doses if still intubated – after prophylaxis may be repeated 6-12 hours later although criteria for retreatment are not specified. In 2000 a large trial of 1,267 babies who met re-dosing criteria (FiO_2 >0.30) were randomised to receive a second dose of bovine surfactant or wait until the FiO_2 reached 0.40[28]. Babies with uncomplicated RDS fared no worse when re-dosed at this higher threshold. Extrapolating these data to make recommendations regarding repeat dosing in the current era of increased non-invasive ventilation use is difficult. The 2008 American Academy of Pediatrics guideline makes no clear recommendation for re-dosing with surfactant[1]. The 2010 European Guideline is also rather non-specific, recommending re-treatment if there is "ongoing evidence of RDS such as the need for mechanical ventilation and supplemental oxygen"[3]. A Canadian Guideline from 2005 makes a fairly specific recommendation that babies should be re-treated if they remain in more than 30% oxygen as early as two hours after the first dose and this is probably what most accurately reflects current UK practice[2].

Conclusion

Although surfactant therapy has been around for a long time, how this important treatment is used has evolved gradually over the years. Initially surfactants were used sparingly and reserved for babies with severe RDS on mechanical ventilation. Gradually clinicians became more comfortable, and at its peak surfactant therapy was used very liberally as prophylaxis in the delivery suite for many babies who perhaps might have managed without. More recently the trend has been to adopt policies of more 'selective' prophylaxis, with early rescue surfactant for the majority of babies with RDS (**FIGURE 2**). This reflects current knowledge about the potential damaging effects of intubation and mechanical ventilation on the preterm lung.

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