

SURFACTANTS. Optimising usage. (Commentary)**Background**

Surfactant is currently used in a number of different strategies for the prevention and the treatment of respiratory distress syndrome (RDS). It may also be used in a number of other conditions other than RDS – these are covered elsewhere. Strategies for surfactant in RDS include:

- **Universal prophylaxis** – where surfactant is administered to all ‘at risk’ infants, with the degree of risk being defined according to gestation at birth. Infants below a certain gestation (this varies according to the institution) receive surfactant as soon as possible after delivery.
- **Targeted selective prophylactic or early treatment** – where antenatal or postnatal screening of amniotic fluid, tracheal or gastric aspirates may target those infants with an immature surfactant profile
- **Selective rescue treatment (early or late)** – infants receive surfactant only if they are ventilated for respiratory failure and where the clinical and/or radiological picture supports the diagnosis of RDS. This is sometimes used in infants who are more mature at birth. Early or late depends on the criteria at which this happens – again this may vary according to the gestation of the infant.

Within each of these strategies for surfactant may be found different strategies of respiratory support that in turn impact on the effectiveness of surfactant and whether further dosing is required or readily undertaken. These might include:

- Intubation and conventional positive pressure ventilation
- Intubation and high frequency oscillation ventilation
- Intubation for the purpose of administering surfactant then elective extubation to nasal CPAP (sometimes called the INSURE [*INtubate SURfactant Extubate*] procedure). This may be electively shortly after birth or at some stage in the first few days after development of respiratory failure with symptoms and signs of RDS
- Elective nasal CPAP (without surfactant) and subsequent rescue surfactant in cases of respiratory failure. After surfactant the infant may be returned to CPAP or may be ventilated for a length of time.
- No respiratory support and treatment after development of respiratory failure with symptoms and signs of RDS

Individualising surfactant treatment according to the infant’s gestation and taking into account risk factors at birth (e.g. the number of antenatal steroid doses, antenatal infection, placental abruption, mode of delivery, etc.) as well as the strategy for the respiratory care in the unit should ensure the optimum use of surfactant. This commentary looks at how these considerations can lead to a better (and perhaps more cost effective) use of surfactant therapy.

Containing the cost of surfactant use

The only surfactant drugs currently on the market are of animal origin and are very expensive. Currently, in the UK, each 100 mg/kg dose for a 1 kg infant costs between £300 and £360. In a 1.5 kg infant the cost of each dose rises to £764 if poractant alfa (Curosurf) is used, although it remains unchanged if beractant (Survanta) is used because this comes in a larger vial). Treatment with poractant alfa becomes even more expensive when an initial dose of 200mg/kg is used (£1528 for the same 1.5 kg infant).

Current policies advocating routine universal prophylaxis for most very preterm infants are, therefore, very expensive. There remains much scope for tailoring usage more closely to need, withholding it where it is not needed, and using it more effectively where it is. Many “*at risk*” infants never develop features of the respiratory distress syndrome (RDS) severe enough to warrant exogenous surfactant; between 32%^[1] and 63%^[2] of infants in the “rescue” arms of the main trials comparing different timing strategies never received any treatment. Even some of the more immature infants <28 weeks gestation can, if carefully managed with early CPAP from the delivery room onwards, be cared for without surfactant.³

Although surfactant drugs seem safe and efficacious there are no data to support their use in infants with a mature surfactant profile at birth. These infants are exposed to a therapeutic agent, that, whilst largely agreed to be safe, is nonetheless of animal origin in many cases and is administered in an invasive manner with the incumbent dangers that go along with intubation. Safe and effective intubation, like most skills, takes time to learn.⁴ Although not widely used in neonatal practice laryngeal masks are used in adult and paediatric resuscitation and have been used to administer surfactant without intubation,⁵ this method, however is yet to be studied in larger randomised controlled trials.

Whilst a prophylaxis strategy for surfactant administration is associated with better outcomes than late rescue therapy,⁶ it may be possible to refine the prophylaxis strategy further to target the population by looking at the maturity of the endogenous surfactant system. The idea of testing for surfactant maturity prior to the birth (or soon after) of the infant confers several advantages, particularly where alternatives to intubation and ventilation can be offered. These tests are not, however, without their own limitations.

Once treated, many infants receive a second (or even third dose) of surfactant because that is '*what it says on the box*'. There is little evidence that the exact timings of the manufacturer's instructions need to be followed to the letter and in many cases RDS improves spontaneously after 48 hours as the infant begins to produce adequate amounts of endogenous surfactant. Whilst re-treatment is frequently given to intubated infants, for those on minimal ventilator settings the necessity of this could be questioned. Equally if the RDS is severe, it makes sense to give the next dose of surfactant earlier rather than later.

Detecting surfactant deficiency

Tests of fetal lung maturity have been used to varying extents in some of the early surfactant studies. Konishi *et al*^{7,8} used the stable microbubble test; Dunn *et al*⁹ used the Lecithin/sphingomyelin (L/S) ratio. Osborn *et al*¹⁰ demonstrated that, in a 'rescue' strategy of surfactant treatment by using the click test they could treat infants with surfactant earlier, and more appropriately, than if they relied on the radiological appearances of RDS. Their surfactant administration times fell from 159 minutes of age to 50 minutes, but importantly their surfactant usage also dropped from 79% to 48% of infants <28 weeks gestation.

Many clinicians believe that surfactant should be administered 'prophylactically' (that is in the delivery room) in order to obtain the greatest clinical benefit,¹¹ the 50 minutes achieved in this study would therefore be unacceptable. This poses a dilemma if amniotic fluid cannot be obtained prior to birth; obtaining postnatal tracheal or gastric aspirates and the performing of the test would also delay surfactant administration.

Verder *et al*¹² recently reported on the collection of gastric aspirates for the stable microbubble test in infants <32 weeks gestation. Samples were obtained at birth in 24% of their population and within 30 minutes of birth for the remainder. Surfactant was required by 39% of infants at a median administration time of 7 hours, whereas RDS (grade 2–3) was seen in 46% of infants as determined by clinical and radiological criteria. Milder (grade 1) RDS was also seen in a further 38% of cases. Unfortunately the analyses of the stable microbubble test were performed retrospectively and therefore did not form part of the clinical decision-making process.

Apart from the difficulties in accessing these tests quickly after birth there is the additional problem that many perform poorly when it comes to the prediction of developing subsequent respiratory problems as many infants with 'immature' surfactant do not develop RDS. Thus simply having immature surfactant is not the whole picture.

Minimising surfactant destruction

The early improvements in oxygenation after surfactant are due to alveolar recruitment and improved functional residual capacity (FRC),¹³ although some improved lung volume may be due to distension of existing functional alveoli rather than recruitment of previously atelectatic ones.¹⁴ Continuous positive airways pressure (CPAP) also increases FRC and its use in the delivery room with or without surfactant has been shown to reduce the need for subsequent ventilation.¹⁵ Increasingly CPAP has successfully been used to manage small preterm infants with RDS,¹⁶ and when combined with surfactant therapy reduced the need for ventilation in infants with moderately severe RDS,¹⁷ especially when administered early or prophylactically.^{18,19} Unfortunately these infants still require intubation to administer the surfactant – the so-called INSURE [INtubate SURfactant Extubate] procedure; and success of this procedure is operator dependent. Even where intubation is successful, not all infants – particularly those of lower gestations – can continue to manage on CPAP.²⁰

High frequency oscillatory ventilation (HFOV) uses a higher mean airway pressure but with cycle volumes that are smaller than the tidal volume of the ventilated infant. It has been shown, compared to conventional ventilation, to limit the development of proteinaceous lung exudates in animals with RDS.²¹⁻²³ In preterm infants <30 weeks gestation early HFOV reduced the need for the second and subsequent doses of surfactant compared to conventional ventilation (30% versus 62%) without any effect on long-term differences in pulmonary outcomes.²⁴ In animal models HFOV with exogenous surfactant reduces lung injury more than if surfactant or HFOV had been used alone,²⁵ and HFOV prolongs the effectiveness of exogenous surfactant.²⁶

Individualised surfactant treatment

Early controlled trials of exogenous surfactant used a variety of dosing intervals, ranging from 1 hour (between the first and second doses of pumactant²⁷) to 12 hours,^{28,29} and a variety of criteria used for selecting which infants received subsequent doses; most of these have been based on oxygen requirements and the need for continued ventilation. Most exogenous surfactants are currently administered at 12 hourly intervals, but occasionally clinical benefit may be seen with more individualised treatment regimes administering the second dose of surfactant early in cases of severe RDS³⁰ or delaying/omitting it in uncomplicated mild RDS.³¹

Kattwinkel *et al*³¹ examined outcomes in 2484 infants treated either prophylactically or with rescue therapy to establish whether there was any difference between a “high” versus “low” threshold for the re-treatment doses. In this randomised trial “low” corresponded a requirement of $\geq 30\%$ oxygen in any ventilated infant. “High” corresponded to ventilation at MAP ≥ 7 cm H₂O and an FiO₂ $\geq 40\%$.

Overall there were no differences between the two arms in any important long-term outcomes. But in a subgroup analysis of infants that had “complicated” RDS (where there was proven or a high risk of sepsis or birth asphyxia) mortality was greater in the ‘high’ threshold arm (34% versus 24%). This outcome probably relates to the fact that infants in the “complicated” subgroup were more likely to have inactivation of their surfactant, thus those in the high threshold arms were more likely to deplete their surfactant stores.

A small group of collaborating neonatologists in Texas recently completed a trial to see whether giving surfactant altered the subsequent evolution of RDS in unventilated infants of ≥ 1250 grams needing 40% oxygen or more when 4-24 hours old.³² They judged such intervention unnecessary and inappropriate.

Higher doses of exogenous surfactant

The estimated pool size of endogenous surfactant in infants recovered from RDS is 100mg/kg.³³ Almost all surfactants are given at a dose of 100mg/kg (see below), but there therefore exists the possibility of administering greater amounts particularly with a smaller volume surfactant such as Curosurf. The UK licence for this surfactant is currently for an initial dose of 100–200mg/kg. Clearly 200mg/kg will cost more than 100mg/kg but it is less clear whether every infant would benefit from a higher initial dose.

Current manufacturers’ recommended and licensed doses (information from manufacturers’ information sheets)

Surfactant		Initial dose	Subsequent doses	Vol (per 100mg)	Dose interval
Poractant alfa	Curosurf	100–200mg/kg	100mg/kg	1.5 ml	6–12 hourly
Beractant	Survanta	100mg/kg	100mg/kg	4 ml	6 hourly
Calfactant	Infasurf	100mg/kg	100mg/kg	3 ml	12 hourly
Bovactant	Alveofact	100mg/kg	100mg/kg	2.4 ml	12 hourly

In one of the largest trials in neonatal medicine, 1069 infants were randomised to a low dose regimen where they were given an initial dose of 100mg/kg and up to 2 further 100mg/kg doses of poractant alfa (Curosurf) and 1099 infants to a high dose regimen (who were given an initial dose of 200mg/kg and then up to 2 further 100mg/kg doses).³⁴ There were no significant differences in any long-term outcomes despite the high dose group being given approximately 140mg/kg more of surfactant (equivalent to over 1 vial of poractant alfa more at a current cost of £382). The authors concluded that, although there were some initial benefits for the higher dose in terms of early oxygen and ventilation, ‘adopting the low dose regimen would lead to considerable cost savings, with no clinically significant loss in efficacy’.

Further evidence in this area also comes from another trial involving poractant alfa.³⁵ The primary intention in this study was to compare outcomes in infants randomised to receive either poractant alfa or beractant but there two groups dosing regimes for poractant alfa – one using an initial 100mg/kg dose and the other an initial 200mg/kg dose. Overall there was no statistically difference in 28 day mortality between the lower (6%) versus the higher dose (3%), but the numbers in the study were small and this was not one of the primary outcomes. Use of 200mg/kg was associated with fewer infants requiring subsequent doses (29% versus 40%); however the total dose for each infant was nearly 100mg/kg greater.

It seems that in most cases 100mg/kg will suffice. A higher initial dose may offer some benefits with earlier improvements in oxygenation and ventilation but not in longer term outcomes. It seems logical therefore to consider that for most infants, doses of 100mg/kg would suffice. In selected cases a higher dose may be advantageous, these would appear to be infants who:

- Are at greater risk of RDS (e.g. those infants whose mother has not received antenatal steroids, born after placental abruption or pre-labour caesarean section)
- Have established RDS (the proportion of surfactant that is inactivated is relatively smaller if a larger dose is used)

- Are being treated using the *INSURE* technique (see above), where subsequent re-dosing would mean re-intubation of the infant

Conclusions

Although surfactant therapy has been shown to be largely safe and efficacious there is no data to support its use in infants with mature surfactant. These infants are exposed to a therapeutic agent, that, whilst largely agreed to be safe, is nonetheless of animal origin in many cases and is administered in an invasive manner with the incumbent dangers that go along with intubation.

Surfactant use can be rationalised in a number of ways. Tests of fetal lung maturity may be used antenatally or soon after delivery to reduce the numbers of infants treated unnecessarily, but most of these tests will still over-estimate the numbers of infants who develop RDS. The tests take time to perform and may delay the administration of surfactant, thus missing the 'window' for optimum timing of surfactant administration. It is not possible to say whether a strategy of selective rescue treatment after using these tests offers better clinical outcomes compared to a prophylactic strategy but it could reduce surfactant usage by over 30%.

Nasal CPAP and HFOV improve the FRC in infants and have been shown to reduce the need for surfactant. Using them with an initial dose of surfactant may further improve outcomes but further study is needed in this area, especially if alternatives to intubation for administration of surfactant are developed.

Most surfactants are given at a dose of 100mg/kg but more can be given if required. In most cases this is probably not necessary but it might be considered if the risk of RDS is high, symptoms and signs of RDS are already established or if re-intubation is to be avoided (e.g. those treated using the *INSURE* technique).

Individualising the surfactant regime to match the infant's disease severity offers perhaps the best and most readily available method to reducing costs but at the same time improving outcomes in those infants with more severe disease. Considering the circumstances surrounding the delivery, the mode of delivery and the treatment strategies ('prophylaxis', '*INSURE*', 'rescue', etc.) should allow the clinician to best predict how to individualise the surfactant regime.

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Tests of fetal lung surfactant maturity

The **lecithin/sphingomyelin (L/S) ratio** was one of the first tests developed.^{1,2} Lecithin (phosphatidylcholine) levels are measured relative to sphingomyelin (a general membrane lipid) using thin layer chromatography. Sphingomyelin levels remain relatively constant throughout fetal development until 32 weeks gestation when they fall, while lecithin levels rise. A value of 2.0 for the L/S ratio (normally achieved from 35 weeks gestation) is generally taken to equate to “mature” surfactant making RDS unlikely. A level of between 1.5 and 2.0 surfactant is considered to show “immaturity”, but the risk of RDS remains low. Below 1.0 the risk of RDS increases.³ The Fetal-Tek 200 (Helena Laboratories, Beaumont Texas, USA) is the most commonly used commercially available method for measuring the L/S ratio in North America⁴ but there are problems with inter-laboratory precision.

One of the major disadvantages of this method is that it is not possible to use this method when amniotic fluid is contaminated by blood or meconium.⁵ Samples for the estimation of the L/S ratio are best collected by amniocentesis; those from vaginal pools – whilst easier to collect – may give a significantly lower (i.e. immature) ratio when compared to a sample obtained by amniocentesis at the same time.⁶ Studies of the L/S ratio show that overall it has good sensitivity but that it lacks specificity; thus it will over-diagnose fetal lung immaturity which could lead to more infants receiving surfactant than would otherwise have developed RDS⁷ Additional disadvantages of the L/S ratio are the requirements for expensive equipment and for trained staff to perform the test, a turn-round time of 3–4 hours, and the current unavailability of the test in many hospitals.

The **stable microbubble test**⁸ can be performed on gastric aspirates or amniotic fluid. A “less than weak” stable microbubble rating (≤ 10 bubbles per mm^3) indicates surfactant deficiency. When testing amniotic fluid it is easy to use and reliable⁹ and said to be 100% predictive on testing amniotic fluid.¹⁰ The sensitivity remains high when tracheal aspirates are used (>90%) but specificity falls to 52%.¹¹ Testing for surfactant maturity using samples other than the amniotic fluid such as gastric aspirates has been found to be even less reliable.^{12,13} The technique can be refined using computerised image analysis.¹⁴

The **TDx assay** is an automated fetal lung maturity test based on fluorescent polarisation to determine the surfactant / albumin ratio.¹⁵ This is the commonest method for determining fetal lung maturity in North America, with Abbott Laboratories commercialising and modifying the early methods to produce their TDx FLM II assay. The test requires less than 1 ml of amniotic fluid, and can be performed in less than 1 hour. A surfactant albumin ratio of 50–70 mg surfactant/g of albumin is considered mature in most studies.^{15,16} Like the L/S ratio and stable microbubble test, the sensitivity is high (almost 100%) but specificity is approximately 70%.¹⁷ Blood contamination may increase the likelihood of obtaining an 'immature' result, but it is not clear whether this statistical difference is important clinically.¹⁸ Similarly samples from vaginal pools may also yield 'immature' results (when compared to amniocentesis samples).¹⁹

The **shake test** and **foam stability index** use the principal that when ethanol is added to amniotic fluid the non-surfactant foam causing substances in amniotic fluid are removed and the stable foam layer that persists after shaking is due to surfactant. In the shake test serial dilutions of ethanol allow the surfactant to be quantified. Unfortunately blood and meconium also render the test invalid. The advantage of the shake test is that it can be performed within 30 minutes. The shake test performs as well as the L/S ratio when screening for RDS,²⁰ but when surfactant is immature or 'transitional' it overestimates the risk of developing RDS.²¹ The foam stability index (FSI) is a variation of the shake test where the highest volume of ethanol that permits the formation of a stable foam ring is expressed as a fraction. This has been developed for commercial use making it simpler, faster and more accessible to the clinician.²² RDS is unlikely with an FSI ≥ 0.47 . Like the shake test blood and meconium render the foam stability index invalid.

The **tap test** is a rapid semi-quantitative measurement of surfactant function.²³ Amniotic fluid is mixed with 6N hydrochloric acid and diethyl ether in a test tube. The tube is tapped briskly 3–4 times to produce 200–300 bubbles in the ether layer. With mature surfactant the bubbles rise to the surface and break down quickly. With immature surfactant the bubbles are stable or break down slowly. The persistence of ≥ 5 bubbles is predictive of surfactant immaturity. Several studies have suggested that the tap test is more reliable than the shake test.^{24,25}

The **click test** is a biophysical test of surfactant function that can be performed on amniotic fluid, tracheal or gastric aspirate samples.²⁶ A 0.2ml sample is added to an equal volume of 95% ethanol in a test tube, which is then shaken in a vortex mixer for 15 seconds. One or 2 drops are then examined under a microscope and the number of bubbles 'clicking' (suddenly shrinking) are counted over a two minute period. No bubbles after 2 minutes indicates immature surfactant. The click test has been shown to be reliable with little inter-observer variability²⁷ and in one study reduced the time to surfactant administration in infants who were not treated prophylactically.²⁸

The **Amniostat-FLM test** is a rapid immunological semi-quantitative agglutination test that can be used to determine the presence of phosphatidylglycerol (PG).²⁹ It can detect PG at a concentration $>0.5 \mu\text{g/ml}$. It takes 20 to 30 minutes to perform, requires only 1.5 ml of amniotic fluid, and is highly sensitive. A positive Amniostat-FLM correlates well with the absence of subsequent RDS and it can be used when samples are contaminated by blood and meconium.³⁰

The **lamellar body count** – taking advantage of the similarity of lamellar body (1–5 μm) and platelet (2–4 μm) sizes permits the use of a standard automated haematological cell counter to quantify the number of lamellar bodies in amniotic fluid.³¹ Normally found in alveolar type II pneumocytes, lamellar bodies are secreted into the alveolar space where they unravel and deposit a layer of surfactant along the alveolar surface. These can also pass into the amniotic cavity and hence are found in amniotic fluid. The lamellar body count, is used to estimate surfactant production in utero and thus predict the degree of fetal lung maturity – counts $>50,000/\mu\text{L}$ suggest fetal lung maturity and $<15,000/\mu\text{L}$ suggest immaturity.³¹

Testing for fetal lung maturity has not really caught on within UK obstetric or neonatal practice. Even in North America where the use of these tests is more widespread the American College of Obstetrics and Gynecology emphasizes that no mature result can completely eliminate the risk of RDS. Part of the problem may be that the same cut-off value for each test is applied to all gestational ages despite the fact that the risk of RDS decreases with increasing gestational age. Testing strategies that incorporate gestational age into predictors of RDS risk may be more practical, and clinically more meaningful, in addressing the dilemma of indeterminate results. Two groups^{32,33} have published risk tables that report risk of RDS at various gestational age-stratified TDx FLM II ratios. Whilst these tests could reduce unnecessary surfactant use it is not clear whether they offer a means to reduce the overall costs of treating a preterm infant.

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