

## PULMONARY SURFACTANTS (Commentary)

### Introduction

Surfactant replacement therapy has revolutionised neonatal respiratory care since its introduction in the 1980s. Along with antenatal steroids, surfactants improve survival for preterm babies and they are now recommended routinely as early in the course of respiratory distress syndrome (RDS) as possible.

Surfactants are also used for conditions other than RDS, such as meconium aspiration, pulmonary haemorrhage and pneumonia, although the evidence base for their use for these indications is much weaker.

Recently, surfactants have been used to deliver steroids directly to the lungs and this seems to be a promising technique worthy of further study.

### Optimising usage

The only surfactant drugs of animal origin currently on the market are very expensive. Currently, in the UK, each 100 mg/kg dose for a 1 kg baby costs between £282 and £306. In a 1.5 kg baby the cost of each dose rises to £547 if Curosurf is used (although it remains unchanged if Survanta is used because this comes in a larger vial). Current policies advocating routine universal prophylaxis for most very preterm babies 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% and 63% of infants in the “rescue” arms of the main trials comparing different timing strategies never received any treatment.<sup>1,2</sup>

While surfactants seem safe and efficacious there are no data to support their use in babies with a mature surfactant profile at birth. Testing an infant for surfactant maturity prior to the birth (or soon after) may confer several advantages, particularly where alternatives to intubation and ventilation can be offered. However, these tests are not without their own limitations.

### Detecting surfactant deficiency

Tests of fetal lung maturity have been used to varying extents in some of the early surfactant studies. Konishi *et al*<sup>3,4</sup> used the stable microbubble test; Dunn *et al*<sup>5</sup> used the Lecithin/Sphingomyelin (L/S) ratio. Osborn *et al*<sup>6</sup> 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 below 28 weeks gestation.

Many clinicians believe that surfactant should be administered ‘prophylactically’ (usually “*in the delivery room*”) in order to obtain the greatest clinical benefit,<sup>7</sup> in which case even the 50 minutes to surfactant administration achieved in the Osborn *et al* study would 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*<sup>8</sup> recently reported on the collection of gastric aspirates for the stable microbubble test in infants below 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),<sup>9</sup> although some improved lung volume may be due to distension of existing functional alveoli rather than recruitment of previously atelectatic ones.<sup>10</sup> 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.<sup>11</sup> Increasingly CPAP has successfully been used to manage small preterm infants with RDS,<sup>12</sup> and when combined with surfactant therapy reduced the need for ventilation in infants with moderately severe RDS,<sup>13</sup> especially when the surfactant is administered early or prophylactically.<sup>14,15</sup> Unfortunately these infants still require intubation to administer the surfactant – the so-called INSURE [INtubate SURfactant Extubate] technique. The success of this procedure is very operator dependent.<sup>16</sup>

CPAP is now widely available and can be applied immediately after birth, either by a nasopharyngeal tube or nasal prong, helping babies to establish their FRC without resorting to immediate intubation or positive pressure ventilation. Babies who develop significant RDS can then be given early rescue surfactant as a semi-elective procedure. Recent studies have attempted to clarify the issues of early respiratory management of very preterm infants.<sup>17-19</sup> However, the results show that the optimum method for managing a preterm infant at risk of RDS is still far from clear. At present it still seems reasonable to administer prophylactic surfactant to extremely preterm infants at high risk of RDS, although a gestational age cut-off should be applied. When deciding who to treat, consideration should also be given to whether or not the mother received antenatal steroid treatment.

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.<sup>20-22</sup> In preterm infants below 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.<sup>23</sup> In animal models HFOV with exogenous surfactant reduces lung injury more than if surfactant or HFOV had been used alone,<sup>24</sup> and HFOV prolongs the effectiveness of exogenous surfactant.<sup>25</sup>

### 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 pumactant<sup>26</sup>) to 12 hours,<sup>27,28</sup> 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 RDS<sup>29</sup> or delaying/omitting it in uncomplicated mild RDS.<sup>30</sup>

Kattwinkel<sup>30</sup> *et al* 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  $\geq 7$  cm H<sub>2</sub>O and an FiO<sub>2</sub>  $\geq 40\%$ .

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 babies of  $\geq 1250$  grams needing 40% oxygen or more when 4-24 hours old.<sup>31</sup> They judged such intervention unnecessary and inappropriate.

Even consensus guidelines still vary in their recommendations; the Canadian guideline makes a fairly specific recommendation that babies should be re-treated if they remain in more than 30% oxygen as early as 2 hours after the first surfactant dose.<sup>32</sup> The European guideline is less specific, recommending re-treatment if there is ongoing evidence of RDS (for example, the need for mechanical ventilation and supplemental oxygen).<sup>33</sup>

### Different doses of surfactants

Almost all surfactants are given at a dose of  $\sim 100$  mg/kg (see below) although there exists the possibility of administering greater amounts particularly with the smaller volume surfactant such as Curosurf.

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

Surfactant	Initial dose	Subsequent doses	Volume per 100mg	Dosing interval
Curosurf	100-200 mg/kg	100 mg/kg	1.5 ml	6-12 hours after 1 <sup>st</sup> dose
Survanta	100 mg/kg	100 mg/kg	4 ml	6 hourly
Infasurf	105 mg/kg	105 mg/kg	3 ml	12 hourly
Alveofact	100 mg/kg	100 mg/kg	2.4 ml	12 hourly

Clearly 200 mg/kg will cost more than 100 mg/kg but it is less clear whether every baby would benefit from a higher initial dose. In one of the largest trials in neonatal medicine, 1069 infants were randomised to a low-dose regimen of Curosurf (starting with an initial dose of 100 mg/kg with up to 2 further 100 mg/kg doses) and 1099 infants to a high-dose regimen (with an initial dose of 200 mg/kg

with up to 2 further 100 mg/kg doses).<sup>34</sup> There were no significant differences in any long-term outcomes despite the high-dose group being given about 140 mg/kg more surfactant (in the case of Curosurf this equates to more than one extra vial; with each vial costing £282). 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 Curosurf.<sup>29</sup> The primary intention in this study was to compare outcomes in infants randomised to receive either Curosurf or Survanta but there were also two dosing regimens for Curosurf – one with an initial dose of 100 mg/kg and the other an initial dose of 200 mg/kg. 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 200 mg/kg was however associated with better short-term outcomes (reductions in oxygen requirements and ventilation) but this did not translate into any longer-term differences.

## 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. Exposing these infants unnecessarily to a therapeutic agent, that, whilst largely safe, is nonetheless of animal origin in many cases and is administered in an invasive manner with all the dangers that accompany intubation should be avoided.

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 may further improve outcomes but further study is needed in this area, especially if alternatives to intubation for administration of surfactant are developed.

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.

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## Tests of fetal lung maturity

Since the early 1970s, fetal lung maturity (FLM) testing has played an important role in identifying neonates at risk of RDS. The various assays, developed in the 1970s and 1980s, maintained their popularity into the 1990s. However, FLM testing has declined as obstetricians and neonatologists have found the results less useful in making a decision about when to time delivery.

The **lecithin/sphingomyelin (L/S) ratio** was one of the first tests developed.<sup>1,2</sup> Lecithin (phosphatidylcholine) levels are measured relative to sphingomyelin, which is a general membrane lipid. 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.<sup>3</sup> 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.<sup>4</sup> Additional disadvantages of the L/S ratio are the requirements for expensive equipment and for trained staff to perform the test and a turn-round time of 3–4 hours.

The **stable microbubble test**<sup>5</sup> can be performed on gastric aspirates or amniotic fluid. A “less than weak” stable microbubble rating ( $\leq 10$  bubbles per mm<sup>3</sup>) indicates surfactant deficiency. When testing amniotic fluid it is easy to use and reliable<sup>6</sup> and said to be 100% predictive on testing amniotic fluid.<sup>7</sup> The sensitivity remains high when tracheal aspirates are used (over 90%) but specificity falls to 52%.<sup>8</sup> Testing for surfactant maturity using samples other than the amniotic fluid such as gastric aspirates has

been found to be even less reliable.<sup>9,10</sup> The technique can be refined using computerised image analysis.<sup>11</sup>

The **TDx-FLM assays** are automated fetal lung maturity tests based on fluorescent polarisation to determine the surfactant:albumin ratio.<sup>12</sup> 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.<sup>12,13</sup> As the demand for tests of FLM have declined so too has the manufacturer's support for this test and have finally led to its withdrawal.<sup>14</sup>

The **shake test** and **foam stability index** use the principle 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,<sup>15</sup> but when surfactant is immature or 'transitional' it overestimates the risk of developing RDS.<sup>16</sup> 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.<sup>17</sup> RDS is unlikely with an FSI  $\geq 0.47$ . 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.<sup>18</sup> 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  $\geq 5$  bubbles is predictive of surfactant immaturity. Several studies have suggested that the tap test is more reliable than the shake test.<sup>19,20</sup>

The **click test** is a biophysical test of surfactant function that can be performed on amniotic fluid, tracheal or gastric aspirate samples.<sup>21</sup> 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 variability<sup>22</sup> and in one study reduced the time to surfactant administration in infants who were not treated prophylactically.<sup>23</sup>

The **Amniostat-FLM test** is a rapid immunological semi-quantitative agglutination test that can be used to determine the presence of phosphatidylglycerol (PG).<sup>24</sup> It can detect PG at a concentration above 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.<sup>25</sup>

The **lamellar body count** has many advantages over traditional methods of determining fetal lung maturity in that it can be performed quickly and is less expensive.<sup>26</sup> The lamellar body count may be performed on a standard laboratory cell counters,<sup>27</sup> but there is a certain degree of reluctance amongst laboratories to run amniotic fluid through their analysers.<sup>14</sup>

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### **Using surfactant for conditions other than neonatal 'RDS'**

When neonatologists talk of respiratory distress or the respiratory distress syndrome (RDS) the problem usually under consideration is that of an immature baby born with a lung as yet unprimed with surfactant. A wide range of conditions can, however, cause acute respiratory distress. Ashbaugh gave a classic description of the key features more than 40 years ago.<sup>1</sup> The acronym used for this alarming and rapidly progressive condition - ARDS - was long considered to stand for *adult*, rather than *acute*, respiratory distress syndrome. This terminology has obscured the fact that rapid progressive hypoxaemic respiratory failure can occur in children needing respiratory support as well as in adults. The very heterogeneity of the condition, and the lack of any uniform terminology, served to limit research for many years. The first widely accepted definition of ARDS was published in 1994 by an American-European Consensus Conference.<sup>2</sup>

Surfactant abnormalities in ARDS were first reported in 1979.<sup>3</sup> Features include a marked reduction in phosphatidylglycerol and in the surfactant associated proteins SP-A, SP-B, SP-C and SP-D, and a fall in the total phospholipid content. There is surfactant inactivation by serum proteins, and the formation and accumulation of fibrin-rich hyaline membranes.<sup>4</sup> Several groups have attempted to treat ARDS with surfactant in the last twelve years. Studies in man<sup>5-25</sup> are summarised in the table printed below. Few of these studies relate to children and none to neonates

## Studies of surfactant preparations in the management of ARDS

Surfactant	Dosage / regimen	Study design	Year	Ref
Colfosceril (Exosurf®)	Continuously aerosolized synthetic surfactant (Exosurf) with DPPC 40.5 mg/ml, or with DPPC 81 mg/ml, or placebo (nebulized 0.6% saline), for up to 5 days	Randomised placebo controlled trial	1992	[5]
Poractant alfa (Curosurf®)	50mg/kg via bronchoscope	Uncontrolled study	1994	[6]
Colfosceril (Exosurf®)	Continuously aerosolized synthetic surfactant (Exosurf) with DPPC 13.5 mg/ml, 175 ml every 4 hours for 12 hours/day or 24 hours/day for 5 days (estimated aerosolized DPPC: 21.9 and 43.5 mg/kg/day respectively), or placebo (nebulized 0.6% saline)	Randomised placebo controlled trial	1994	[7]
Colfosceril (Exosurf®)	240ml of 13.5mg/ml nebulised over 24 hours for up to 5 days	Randomised placebo controlled trial	1996	[8]
Bovactant (Alveofact®)	300mg/kg via bronchoscope	Uncontrolled study	1996	[9]
Beractant (Survanta®)	50mg/kg (8 doses) or 100mg/kg (4 or 8 doses) via an endotracheal tube	Randomised placebo controlled trial	1997	[10]
Calfactant (Infasurf®)	2800 mg/m <sup>2</sup> via an endotracheal tube	Randomised placebo controlled trial (children)	1997	[11]
Lucinactant (Surfaxin®)	Bronchoscopic administration of 30ml of 2.5mg/ml followed by suction then 30ml of 10mg/ml (group 1), 2 x 30ml of 2.5mg/ml followed by suction then 30ml of 10mg/ml (group 2), 2x 30ml of 2.5mg/ml followed by suction then 30ml of 10mg/ml ± repeat doses (group 3)	Uncontrolled study sequential groups (1-3)	1999	[12]
Poractant alfa (Curosurf®)	50mg/kg at 6-24 hourly intervals or 200mg/kg x 9 doses via an endotracheal tube	Uncontrolled study (children)	1999	[13]
Lusulptide (Venticute®)	50mg/kg x 4 (low dose) or 200mg/kg followed by 100mg/kg x 3 via an endotracheal tube	Randomised placebo controlled trial	2000	[14]
HL10	Intratracheal porcine surfactant (HL10) with 100-200 mg/kg of phospholipids, up to 4 doses, or standard therapy	Randomised placebo controlled trial	2001	[15]
Poractant alfa (Curosurf®)	3ml of 5mg/ml via bronchoscope	Uncontrolled study (children and adults)	2002	[16]
Bovactant (Alveofact®)	300-500 mg/kg via bronchoscope	Uncontrolled study	2002	[17] [18]
Lusulptide (Venticute®)	25mg/kg x 4 (low dose) or 50mg/kg x 4 (high dose) via an endotracheal tube	Randomised placebo controlled trial	2003	[19]
Bovactant (Alveofact®)	100mg/kg via an endotracheal tube ± repeat doses	Randomised placebo controlled trial (children)	2003	[20]
Beractant (Survanta®)	150mg/kg an endotracheal tube x2 at 12 hourly intervals	Uncontrolled study (children)	2003	[21]
Lusulptide (Venticute®)	50mg/kg via an endotracheal tube with up to 3 repeat doses at 4 hourly intervals in first 24 hours	Randomised placebo controlled trial	2004	[22]
Calfactant (Infasurf®)	intratracheal instillation of 2 doses of 80 mL/m <sup>2</sup> calfactant (or placebo) administered 12 hours apart	Randomised placebo controlled trial (infants, children, and adolescents)	2005	[23]
Surfactant BL	3 mg/kg twice a day via bronchoscope	Historical controls. All patients post-cardiac surgery	2006	[24]
HL-10	Up to three dose of 200 mg/kg administered as intratracheal bolus	Randomised placebo controlled trial	2009	[25]

Overall studies of surfactant in ARDS show some benefits in terms of oxygenation and ventilation, but these are temporary and a meta-analysis of the available randomised controlled trials fails to demonstrate any improvement in mortality.<sup>26</sup> This may reflect the diverse pathologies leading to ARDS, particularly in the older population.

Few patients in these studies were children<sup>11,13,16,20,21,23</sup> and fewer still were babies. Nevertheless, although the term ARDS is not widely used in neonatology, several neonatal conditions – all involving alveolar injury, protein exudation, surfactant inhibition, and a vicious cycle of worsening injury – fulfil the criteria for ARDS. These are meconium aspiration syndrome, congenital pneumonia and sepsis (especially Group B *Streptococcal* infection) and bronchiolitis. Similar problems can be triggered in pulmonary hypoplasia. The following is a summary of those conditions in infancy (other than primary surfactant deficiency or 'RDS') where the potential value of treatment with surfactant has been studied.

Many different surfactant products have been developed, and a range of commercial products have been, or still are, available (see Appendix 1). It should be borne in mind that just because one surfactant preparation has been shown to be beneficial in treating one respiratory condition, it does not automatically mean that all surfactant preparations will be equally effective.

### Meconium aspiration syndrome

Meconium aspiration syndrome (MAS) is an important cause of respiratory distress in the term and post-term infant with a reported incidence of 2 per 1000 live births in developed countries.<sup>27</sup> The clinical picture is one of early onset of respiratory distress in the context of meconium stained amniotic fluid (occurring in nearly 20% of live births<sup>28</sup>) and, usually, perinatal compromise due to hypoxia or infection. Inhalation of meconium can cause a severe form of aspiration pneumonitis leading to mechanical airway obstruction, surfactant inactivation and secondary atelectasis.<sup>29</sup> Histologically there is meconium in the airways with hyaline membrane formation due to epithelial necrosis and protein exudation. Meconium has an extremely high surface tension (215 mN/m)<sup>30</sup> and has been shown to have a dose-dependent inhibitory effect on the surface tension lowering property of surfactant.<sup>31</sup> A high concentration of surfactant can overcome this inhibitory effect,<sup>32</sup> but it is also clear that some surfactants are more affected by meconium more than others. Recombinant hydrophobic surfactant proteins or synthetic analogues of these proteins can, in addition, be used to produce surfactant preparations that are relatively resistant to inactivation.<sup>33</sup> Many babies with severe meconium aspiration die, but this is largely because many also have a neonatal encephalopathy (hypoxic ischaemic encephalopathy). Others develop pulmonary hypertension, a complication treatable with inhaled nitric oxide, but sometimes requiring extracorporeal membrane oxygenation (ECMO).<sup>34,35</sup>

The response in a number of uncontrolled studies using various preparations of unaltered exogenous surfactants (calfactant<sup>36</sup>, bovactant<sup>37</sup>, bovine lung surfactant extract<sup>38</sup>, poractant alfa<sup>39,40</sup> and beractant<sup>41</sup>) was mixed and rather unpredictable: the condition of some infants improved but in others it did not. Two randomised controlled trials<sup>42,43</sup> – both using beractant (Survanta) – showed that surfactant can reduce the risk of a pneumothorax and the need for ECMO, but treatment in term infants with meconium aspiration did not improve overall mortality. A more recent study using poractant alfa (Curosurf) again showed early improvements in ventilation and oxygenation but no reduction in the duration of ventilation or in mortality.<sup>44</sup> Surfactant administration improved lung function in infants already on ECMO, and decreased the time on ECMO, but it was of little other long term benefit.<sup>43</sup>

The amount of surfactant administered in these studies was similar to the amount traditionally given in classic RDS due to primary surfactant deficiency, and it may be that a larger or a more frequent dose is needed to overcome the inhibitory effect that meconium has on surfactant's ability to lower surface tension. In one animal model, large doses of an animal-derived surfactant improved ventilation and pulmonary compliance<sup>45</sup> and, in another, a continuous infusion of Survanta via a side-port at a dose of 4ml/kg over 1 hour improved oxygenation and lung compliance more than a single bolus containing the same total dose.<sup>43</sup> With the need for higher doses of surfactant in mind, a fourth randomised study of exogenous surfactant used 150 mg /kg/dose of beractant for up to 3 doses.<sup>46</sup>

Meta-analysis of the four randomised placebo-controlled studies,<sup>47</sup> showed no difference in mortality but did show a reduction in both the need for rescue using ECMO and the duration of hospitalisation in treated babies.

Whilst exogenous surfactant improves short-term outcomes, it is apparent that inhibition by meconium, blood and protein is a problem that needs to be addressed; there are three potential ways of countering the inhibitory effect of meconium on surfactant. The **first** is to supplement the amount of the surfactant proteins SP-B and SP-C present in surfactant.<sup>48</sup> When this technique was explored in a rat model of RDS (not meconium aspiration) the administration of a synthetic polypeptide analogue of surfactant protein SP-B seemed beneficial.<sup>49</sup> There are no reports of the use of this approach in the care of the human infant with meconium aspiration as yet.

A **second** is to remove meconium by lung lavage. When this was first studied in the mid 1970's,<sup>50</sup> saline was used, which further added to the surfactant dysfunction. Saline lavage followed by surfactant administration was later reported in one small study.<sup>51</sup> More recently lavage using dilute surfactant has been studied in animals,<sup>52-57</sup> in observational studies<sup>58,59</sup> and, more recently, in two small randomised controlled trials.<sup>60,61</sup> Although animal work was promising, there has been concern that these models

do not replicate the compromised cardiac status seen in newborn infants with meconium aspiration syndrome.<sup>62,63</sup> In the earlier randomised trial 20% of the children treated with lavage developed significant hypoxaemia and/or hypotension during treatment.<sup>60</sup> Two large randomised multicentre trials using Surfaxin (KL4-surfactant) in the treatment of RDS have now been reported,<sup>64,65</sup> and the product in question may soon get a license for clinical use in America. Large volume lavage (15 ml/kg) using dilute beractant (5mg/ml) was investigated in a recently completed randomised controlled trial; whilst there was no difference between treated infants and controls in terms of their requirements for respiratory support; but fewer infants who underwent lavage died or required ECMO (3/30 compared with 11/35 in the control group).<sup>61</sup>

A **third** experimental approach involves the use of polymers, such as polyethylene glycol (PEG) or dextran, because these are known to reduce surfactant inhibition.<sup>66-68</sup> No human trials have been published as yet, and safety concerns currently remain unaddressed because PEG is a polymer of ethylene glycol which is known to be potentially toxic – particularly in the preterm baby. However, while low molecular weight PEGs (below 400) may be potentially toxic, the Federal Drug Administration in America has approved high molecular weight PEG for internal human consumption. PEG is also used for compounding many drugs and cosmetic products and has also been investigated (bound with free haemoglobin) as a blood substitute.<sup>69</sup>

However, while all these strategies appear promising, they are all still experimental. All still await evaluation in controlled trials of adequate size. No discussion of these possibilities should be allowed to obscure the fact that babies with meconium aspiration should not be ventilated at all if possible, and that those who remain hypoxaemic despite ventilation are ideal candidates for ECMO treatment.<sup>70</sup> This strategy ensures adequate oxygenation while providing time for the pulmonary vasculature and parenchyma to recover without further barotrauma. The UK collaborative ECMO trial, which recruited infants with an oxygenation index of over 300 (40 if partial pressure is measured in mmHg), showed that, with ECMO treatment, there was one extra survivor for every four children so treated.<sup>71</sup>

### Neonatal sepsis and pneumonia

Like meconium aspiration, pneumonia and sepsis cause surfactant inactivation, an influx of serum protein into the alveoli and the formation of hyaline membranes. In theory therefore surfactant replacement ought to be beneficial. The surfactant proteins SP-A and SP-D, present in endogenous surfactant (i.e. the body's own surfactant), play an important role in the lung's innate immune response to infection.<sup>72</sup> However exogenous surfactant preparations that do not contain these proteins have also been shown to reduce bacterial proliferation in an animal model of Group B *Streptococcal* pneumonia.<sup>73</sup> Prophenins – derivatives of the cathelicidin antibacterial peptides – have been found in porcine surfactant, and these are preserved by the usual methods used to extract animal-derived lung surfactants.<sup>74</sup> It is possible, therefore, that they are responsible for some of the putative antibacterial action of exogenous surfactants. There is also evidence to suggest that SP-C may play a major role in the restoration of lung function in ARDS. When different surfactant products were compared rSP-C (Venticute) and bLES were shown, in a rat lung lavage model of ARDS, to improve oxygenation more than Infasurf and Alveofact.<sup>75</sup> The authors of this study speculated that this was because of the higher levels of SP-C (bLES has 3 times as much SP-C as Infasurf and Alveofact).<sup>76</sup>

Exogenous surfactants have also been shown to improve gas exchange in affected infants.<sup>77,78</sup> Although mortality in this group of sick infants remained very high, the greatest improvement was seen in those given high dose treatment at frequent intervals.<sup>78</sup> In a randomised trial in term infants with a mixture of meconium aspiration syndrome and pneumonia, treatment with Survanta significantly reduced the need for ECMO without increasing complications.<sup>79</sup> Much remains to be learnt about the optimum dose to give, optimum treatment frequency and the right number of doses to give but most studies suggest that, as in meconium aspiration syndrome, these babies need substantially more surfactant than those born with simple surfactant deficiency (classic 'RDS').

### Congenital diaphragmatic hernia and pulmonary hypoplasia

The outcome in infants with congenital diaphragmatic hernia (CDH) remains poor despite advances in neonatal care.<sup>80</sup> Treatment with inhaled nitric oxide, liquid ventilation and ECMO is of limited value in babies with severe pulmonary hypoplasia, and even fetal surgery is not yet of any proven value. While experimental studies have shown that there is surfactant immaturity in congenital diaphragmatic hernia,<sup>81</sup> treatment with exogenous surfactant only improves oxygenation to a minimal degree.<sup>82</sup> There does not appear to be any benefit to routine use of surfactant either in term infants with CDH<sup>83</sup> or in term infants with CDH already on ECMO.<sup>84</sup> In preterm infants with CDH surfactant may even worsen outcome.<sup>85</sup> Therefore surfactant use in CDH should be restricted to term infants with radiological or biochemical evidence of surfactant deficiency.

## Bronchiolitis

Babies with respiratory syncytial virus (RSV) bronchiolitis have less surfactant in their lungs than normal, and the surface tension lowering ability of what surfactant there is seems to be impaired.<sup>86,87</sup> Exogenous surfactant has been shown to improve both oxygenation and ventilation of severely affected infants needing respiratory support.<sup>88</sup> In three randomised trials (all using an animal-derived surfactant)<sup>89-91</sup> babies treated with surfactant did not show the progressive deterioration of compliance and resistance that was seen in the control group. In the largest of these studies treatment with surfactant reduced the amount of time the child spent on a ventilator, and the time spent in intensive care.<sup>91</sup> Meta-analysis of the three studies reported no effects on mortality and suggested it is only appropriate to give surfactant to a small number of babies with particularly severe bronchiolitis.<sup>92</sup> Further studies are going to be needed before we have any clear idea of how much surfactant these babies need, when it is that they need it or how often they need it.

## Pulmonary haemorrhage

Early surfactant studies reported an increase in pulmonary haemorrhage after surfactant treatment; much of this, it was postulated, was due to pulmonary oedema and patent ductus arteriosus. Blood is a potent inhibitor of surfactant, and exogenous surfactant may be useful in reversing the inhibition and improving lung function after haemorrhage irrespective of the cause.<sup>93,94</sup> Data pertaining to dosages and frequency of treatment are lacking due to the absence of randomised controlled trials which are difficult to perform because of the unpredictable nature of the problem.

## Chronic lung disease of prematurity (broncho-pulmonary dysplasia)

Chronic lung disease of prematurity (broncho-pulmonary dysplasia or BPD) is a common problem in the ventilated preterm infant. There are decreases in levels of surfactant proteins in preterm infants who continued to be ventilated beyond 7 days of age.<sup>95</sup> These decreases were similar to those seen in adults with ARDS.<sup>17</sup> Various mechanical and biochemical insults, particularly infection, lead to inflammation and then to transient surfactant inhibition and dysfunction. However, just as in ARDS, surfactant can lead to temporary improvements in lung function but does not improve overall mortality.<sup>96</sup>

A novel use for surfactant in relation to chronic lung disease of prematurity is in the use of surfactant as a vehicle for the administration of steroids directly to the lungs. In a pilot study, 116 VLBW infants with severe RDS were randomised to receive either 8-hourly beractant 100 mg/kg or beractant with added budesonide 0.25 mg/kg. The combined outcome of death/BPD was significantly reduced in the budesonide group in this small study.<sup>97</sup> This technique requires further study in a larger trial designed to see if this apparent benefit is real.

## Conclusions

Surfactant therapy may be a useful in many conditions causing respiratory failure in the neonatal period and beyond. In neonatal RDS there is simple surfactant deficiency, but in these other conditions there is surfactant inactivation, and any process causing endogenous surfactant inactivation will almost certainly also tend to inactivate any exogenous surfactant that is given. The optimum treatment strategy remains unclear, but these babies almost certainly need more surfactant than the average preterm baby with 'simple' RDS. Animal-derived products are currently the treatment of choice, but synthetic products containing protein analogues may, in time, turn out to be equally, if not more, effective. The protein content of products of animal origin is hard to standardise; in the future it should be possible to manufacture surfactant with a higher and more consistent protein level in the products that are at present available.

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## Appendix I. Exogenous surfactant preparations reported in the medical and scientific literature

Chemical name	Trade name	Source	Proteins
<b>Protein-free synthetic surfactants</b>			
Nebulised DPPC <sup>1,2</sup>			
Pumactant <sup>3</sup>	ALEC <sup>®</sup>		
Colfosceril <sup>4</sup>	Exosurf <sup>®</sup>		
Turfsurf <sup>5</sup>			
Aposurf <sup>6</sup>			
<b>Animal derived surfactants</b>			
<b>(a) minced lung extracts</b>			
Poractant alfa <sup>7</sup>	Curosurf <sup>®</sup>	porcine	SP-B and SP-C
Surfactant CK <sup>8</sup>		"	SP-B and SP-C
HL-10 <sup>9</sup>		"	SP-B and SP-C
Butantan surfactant <sup>10</sup>		"	SP-B and SP-C
Surfactant TA <sup>11</sup>	Surfacten <sup>®</sup>	bovine	SP-B and SP-C
Beractant <sup>11</sup>	Survanta <sup>®</sup>	"	SP-B and SP-C
Newfactan <sup>12</sup>		"	SP-B and SP-C
Surfactant BL <sup>13</sup>		"	SP-B and SP-C
<b>(b) lung lavage surfactant extracts</b>			
Bovactant <sup>14</sup>	Alveofact <sup>®</sup>	bovine	SP-B and SP-C
Calfactant <sup>15</sup>	Infasurf <sup>®</sup>	"	SP-B and SP-C
CLSE <sup>16</sup>	bLES <sup>®</sup>	"	SP-B and SP-C
Surfacen <sup>17</sup>		porcine	SP-B and SP-C
<b>Human surfactant</b>			
Amniotic fluid-derived <sup>18</sup>		human	SP-A, SP-B and SP-C (?SP-D)
<b>Surfactants with synthetic / recombinant proteins</b>			
Lucinactant (sinapultide) <sup>19</sup>	Surfaxin <sup>®</sup>		KL4
Dimeric SP-B polypeptide <sup>20</sup>			Dimeric SP-B1-25
Mini-B <sup>21</sup>			34-residue polypeptide based on SP-B N- and C- terminal regions
Recombinant SP-C (Iusulptide) <sup>22</sup>	Venticute <sup>®</sup>		rSP-C
and SP-C analogues, <sup>23</sup> SP-C33, <sup>24</sup> and SP-C(LK) <sup>25</sup>			
SP-A analogues <sup>26</sup>			
SP-D (truncated fragment) <sup>27</sup>			

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