

**SURFACTANTS. Indications for use** (Commentary)**Using surfactant for conditions other than neonatal 'RDS'**

When neonatologists talk of respiratory distress or the respiratory distress syndrome (RDS) it is the problem seen in an immature baby born with a lung as yet unprimed with surfactant that is usually under consideration. A wide range of conditions can, however, cause acute respiratory distress. Ashbaugh gave a classic description of the key features more than 35 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>5-22</sup> are summarised in the table printed overleaf. Few of these studies are studies relate to children and none to neonates

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>23</sup> This may reflect the diverse pathologies leading to ARDS in the older population. Few of the patients in these studies were children<sup>11,13,16,20,21</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 now been developed, and a range of commercial products have been, or still are, available (see Appendix I).

**Meconium aspiration**

Meconium aspiration is a severe form of aspiration pneumonitis causing mechanical airway obstruction, surfactant inactivation and secondary atelectasis.<sup>24</sup> Histologically there is meconium in the airways with hyaline membrane formation due to epithelial necrosis and protein exudation. Meconium has been shown to have a dose-dependent inhibitory effect on the surface tension lowering property of surfactant. A high concentration of surfactant can overcome this inhibitory effect,<sup>25</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>26</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>27,28</sup>

The response in two uncontrolled studies using an unaltered exogenous surfactant was mixed and rather unpredictable: some infants became less oxygen dependant but other did not.<sup>29,30</sup> Two randomised controlled trials<sup>31,32</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, as a meta-analysis of the two trials has also confirmed.<sup>33</sup> 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>34</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>32</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>35</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>32</sup> Findlay *et al*<sup>31</sup> used this technique in their study.

## Studies of surfactant use in ARDS

Surfactant	Trade name	Dosage / regimen	Study design	Year	Ref
Colfosceril	Exosurf <sup>®</sup>	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 <sup>®</sup>	50mg/kg via bronchoscope	Uncontrolled study	1994	[6]
Colfosceril	Exosurf <sup>®</sup>	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 <sup>®</sup>	240ml of 13.5mg/ml nebulised over 24 hours for up to 5 days	Randomised placebo controlled trial	1996	[8]
Bovactant	Alveofact <sup>®</sup>	300mg/kg via bronchoscope	Uncontrolled study	1996	[9]
Beractant	Survanta <sup>®</sup>	50mg/kg (8 doses) or 100mg/kg (4 or 8 doses) via an endotracheal tube	Randomised placebo controlled trial	1997	[10]
Calfactant	Infasurf <sup>®</sup>	2800 mg/m <sup>2</sup> via an endotracheal tube	Randomised placebo controlled trial (children)	1997	[11]
Lucinactant	Surfaxin <sup>®</sup>	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 <sup>®</sup>	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]
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]
Poractant alfa	Curosurf	3ml of 5mg/ml via bronchoscope	Uncontrolled study (children and adults)	2002	[16]

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>36</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>37</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>38</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>39</sup> More recently lavage using dilute surfactant has been studied in animals,<sup>40-45</sup> in observational studies<sup>46,47</sup> and, more recently, in a small randomised controlled trial.<sup>48</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>49,50</sup> In the randomised trial 20% of the children treated with lavage developed significant hypoxaemia and/or hypotension during treatment.<sup>48</sup> Two large randomised multicentre trials using Surfaxin (KL4-surfactant) have now been reported,<sup>51,52</sup> and the product in question may soon get a license for clinical use in America.

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>53-54</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 (< 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>56</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>57</sup> This strategy ensures adequate oxygenation while providing time for the pulmonary vasculature and parenchyma to recover without further barotrauma. The collaborative UK 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>58</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>59</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>60</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>61</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>62</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).

Exogenous surfactants have also been shown to improve gas exchange in affected infants.<sup>63,64</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>65</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>66</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>67</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>68</sup> treatment with exogenous surfactant only improves oxygenation to a minimal degree.<sup>69</sup> There does not appear to be any benefit to routine use of surfactant either in term infants with CDH<sup>70</sup> or in term infants with CDH already on ECMO.<sup>71</sup> In preterm infants with CDH surfactant may even worsen outcome.<sup>72</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>73,74</sup> Exogenous surfactant has been shown to improve both oxygenation and ventilation of severely affected infants needing respiratory support.<sup>75</sup> In three randomised trials (all using an animal-derived surfactant)<sup>76-78</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>78</sup> Clearly it is only appropriate to give surfactant to a small number of babies with particularly severe bronchiolitis. Further studies are going to be needed before we have any clear idea of how much surfactant these babies need, 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>79</sup> Data pertaining to dosages and frequency of treatment are lacking.

### Chronic lung disease of prematurity (Bronchopulmonary dysplasia)

Chronic lung disease of prematurity (Bronchopulmonary dysplasia) 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>80</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>81</sup>

### 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. It should be more consistent in the products containing synthetic proteins that are at present under development.

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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
<b>(b) lung lavage surfactant extracts</b>			
Bovactant <sup>12</sup>		Alveofact <sup>®</sup>	bovine
Calfactant <sup>13</sup>	Infasurf <sup>®</sup>	"	SP-B and SP-C
CLSE <sup>14</sup>	bLES <sup>®</sup>	"	SP-B and SP-C
<b>Human surfactant</b>			
Amniotic fluid-derived <sup>15</sup>		human	SP-A, SP-B and SP-C (?SP-D)
<b>Surfactants with synthetic / recombinant proteins</b>			
Lucinactant (sinapultide) <sup>16</sup>	Surfaxin <sup>®</sup>		KL4
Dimeric SP-B polypeptide <sup>17</sup>			Dimeric SP-B1-25
Recombinant SP-C (Iusulptide) <sup>18</sup>	Venticute <sup>®</sup>		rSP-C
and SP-C analogues, <sup>19</sup> SP-C33, <sup>20</sup> and SP-C(LK) <sup>21</sup>			
SP-A analogues <sup>22</sup>			
SP-D (truncated fragment) <sup>23</sup>			

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