

Highlights of  
a Satellite Symposium  
at the  
44<sup>th</sup> Annual Meeting  
of the European Society  
for Paediatric Research (ESPR)



Bilbao, Spain  
September 27–30, 2003

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**SURFACTANT STATE OF THE ART  
AND FUTURE DEVELOPMENTS**

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## SURFACTANT STATE OF THE ART AND FUTURE DEVELOPMENTS

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## SURFACTANT STATE OF THE ART AND FUTURE DEVELOPMENTS

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### Contents

---

5  
Introduction

---

6  
New surfactant features and future proteins and biophysics  
Jesús Pérez-Gil

---

10  
The INSURE approach: does nCPAP and surfactant work only for Vikings?  
Mats Blennow

---

13  
CPAP and prophylactic surfactant  
Merran Thomson

---

17  
Concluding remarks  
Henry Halliday

---

---

## Abbreviations

a/APO <sub>2</sub>	arterial to alveolar oxygen tension ratio
BAL	bronchoalveolar lavage
BPD	bronchopulmonary dysplasia
BW	body weight
CLD	chronic lung disease
CPAP	continuous positive airway pressure
GA	gestational age
FiO <sub>2</sub>	fraction of inspired oxygen
FRC	functional residual capacity
HMD	hyaline membrane disease
IPPV	intermittent positive pressure ventilation
IVH	intraventricular haemorrhage
MV	mechanical ventilation
nCPAP	nasal continuous positive airway pressure
NICU	neonatal intensive care unit
PaO <sub>2</sub>	partial pressure of arterial oxygen
PaCO <sub>2</sub>	partial pressure of carbon dioxide
PIE	pulmonary interstitial emphysema
PTX	pneumothorax
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
VLBW	very low birth weight





## Introduction

Bilbao with its futuristic museum was an entirely appropriate venue for this symposium entitled 'Surfactant State of the Art and Future Developments'. Surfactant research has come a long way since 1959 when Avery and Mead first reported that saline extracts from lungs of preterm infants with RDS lacked the low surface tension characteristic of pulmonary surfactant. Today surfactant therapy based on sound physiological principles and extensive experimental and clinical testing represents a major advance in reducing mortality in preterm infants. Natural pulmonary surfactants with their excellent tolerability and improved efficacy are now the agents of first choice in the management of respiratory problems in preterm infants.

This symposium was designed to bring together experts from around Europe to discuss some of the latest findings in pulmonary surfactant therapy. The opening presentation entitled 'New surfactant features and future proteins and biophysics' by Jesús Pérez-Gil, from Madrid, discusses the development of working models to identify the diverse components of the surfactant complex and to characterise their functions with the aim of developing new more effective surfactants. Mats Blennow presents results from his group in Stockholm on the reduction in the need for MV using the INSURE (INTubation-SURfactant-Extubation: INSURE) approach and how these results are reproduced in other patient populations. Merran Thomson, from London, outlines the rationale for the use of nCPAP in combination with prophylactic surfactant, presents data from clinical trials and from a new animal model of BPD and suggests a strategy for the use of nCPAP and prophylactic surfactant based on the stage of lung development.

Professor Halliday, from Belfast, in his summing up outlines the recommended protocol for surfactant use depending on GA. In infants with a GA of 27–28 weeks, prophylaxis with a natural surfactant (100 mg/kg) is recommended. In those of 29–31 weeks early nCPAP with early rescue with natural surfactant (100 mg/kg) is the treatment of choice, while observation is advised in those with a GA  $\geq 32$  weeks.



# New surfactant features and future proteins and biophysics

Jesús Pérez-Gil

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## Pulmonary surfactants — structure and function

Pulmonary surfactant, a lipid-protein complex that modulates surface tension at the respiratory air-liquid interface to stabilise bronchoalveolar structure, plays a fundamental role in lung development and respiration. RDS, characterised by a deficiency of surfactant, affects over half of premature infants and accounts for the largest single group of babies admitted to NICUs. This presentation discusses the development of working models to identify the diverse components of the surfactant complex and to characterise their functions with the ultimate aim of developing new and more effective surfactant molecules.

Using BAL to separate the native surface-active fraction of surfactant, it is possible to identify and purify the molecular components contained in the surfactant complex. We now know that for a surfactant to function effectively two properties are essential:

- Good compressibility to reach low surface tensions under pressure, on expiration
- Rapid interface adsorption, on inspiration<sup>[1,2]</sup>.

## Composition of human surfactant

Phospholipids, which make up over 80% of surfactant complexes, play a major biophysical role in surfactant function because of their ability to form stable interfacial monomolecular films that are able to achieve and sustain very low surface tensions. Dipalmitoylphosphatidylcholine (DPPC, 41%) contains two saturated acyl chains that can be tightly packed during compression allowing high density at the interface, thus reducing surface tension to near zero. Unsaturated phosphatidylcholine species (PC, approx. 25%) increase the fluidity of surfactant bilayers to permit DPPC to undergo complex and dynamic transformations associated with transfer of surfactant to the air-liquid interface. Negatively charged phospholipids like phosphatidylglycerol (PG) or phosphatidylinositol (PI) in the order of 8% by weight are also essential to optimise disposition and lipid-protein interactions of the hydrophobic surfactant-associated proteins<sup>[3]</sup>. It was previously thought that for surfactants to effectively reach the lowest surface tensions they had to produce interfacial films highly enriched with DPPC. We now know that lateral organisation of DPPC, PC and other lipids and molecules may take place without molecular refining, producing a stable structure able to sustain very low surface tensions at the end of expiration.

## Structure and function of lung surfactant proteins

Surfactant complexes contain approximately 8% by weight of specific proteins. Four classes of surfactant-associated proteins have been identified: the hydrophobic proteins SP-B and SP-C and the hydrophilic SP-A and SP-D. SP-B and SP-C are surface-activity catalysers required for surfactant activity, including:

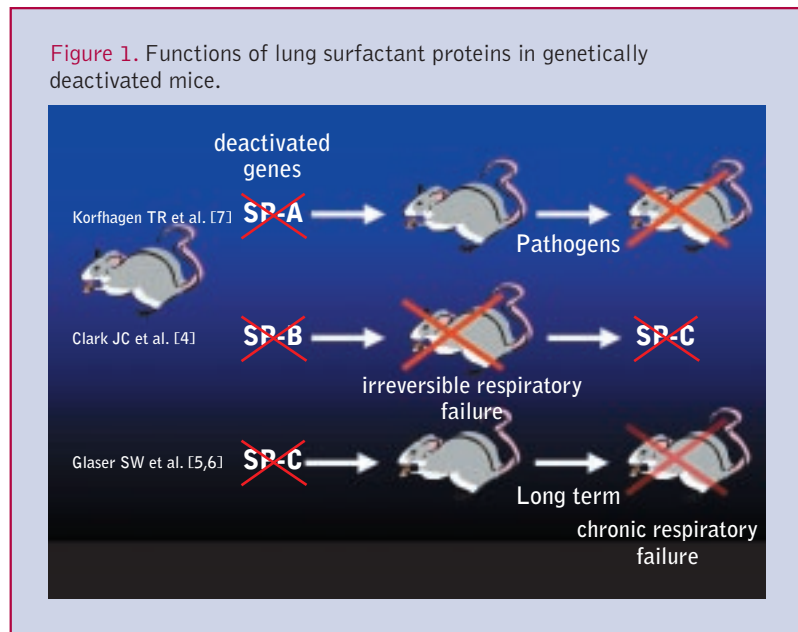
- assembly of surfactant structures such as lamellar bodies, tubular myelin or surface reservoirs
- bilayer-to-monolayer transitions
- modulation of viscoelastic properties of the interfacial films.



In general terms, SP-B and SP-C are essential to promote transfer of surface-active complexes to the interface and to modulate the physical properties of the surfactant film under the dynamic conditions imposed by respiration.

The development of animal models in which expression of surfactant-active proteins has been genetically deactivated has allowed a precise analysis of the function of the individual proteins. SP-B is shown to be the most important, with a deficiency of SP-B causing irreversible respiratory failure<sup>[4]</sup> (Figure 1). Deactivation of SP-B also causes lack of mature SP-C, indicating that processing and assembly of both hydrophobic proteins is somehow

interconnected. SP-C by itself does not seem to be strictly required to initiate respiratory function at birth<sup>[5]</sup>. However, surfactant obtained from the lungs of SP-C knock-out mice seems to be intrinsically unstable at low volumes of the lung and in the long term, genetic deficiencies in the structure and expression of the SP-C gene cause chronic respiratory failure<sup>[6]</sup>. Other animal models also indicate that the hydrophobic proteins SP-A and SP-D have no apparent effects on respiratory function but contribute to host defence against invading pathogens<sup>[7,8]</sup>.



## Therapeutic surfactants preparations

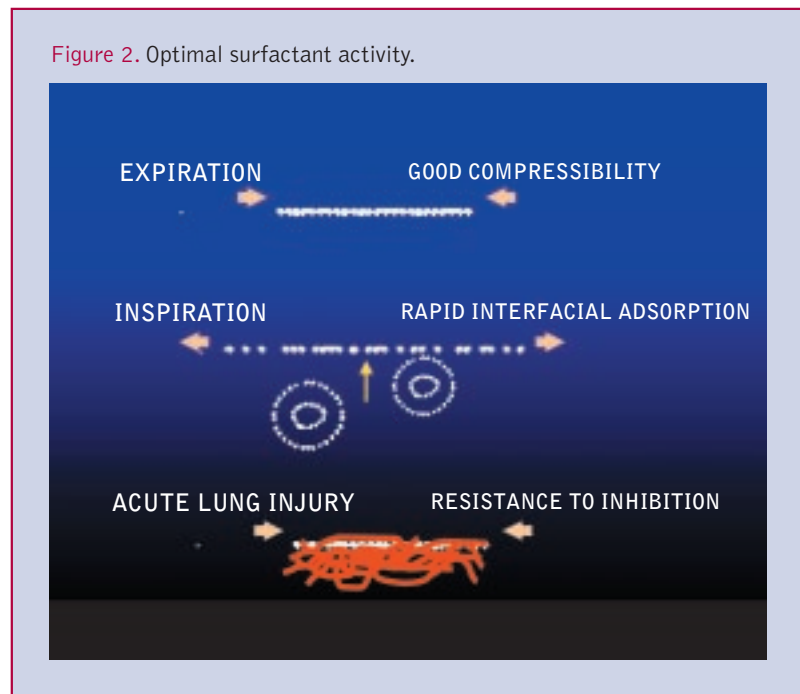
There are two main types of therapeutic surfactants preparations: those obtained from natural sources and those of an entirely synthetic composition. Although all the preparations contain phospholipids and hydrophobic peptides or proteins, there are important structural and functional differences. Natural surfactant preparations, for example poractant alfa (Curosurf<sup>®</sup>, Chiesi Farmaceutici), are obtained from animal lungs and contain phospholipids (DPPC, PC, PG, PI) isolated from the native surface-active surfactant fraction (large aggregates) plus the two hydrophobic surfactant-associated proteins (SP-B, SP-C). Synthetic surfactant preparations contain phospholipids and synthetic/recombinant peptides or proteins designed to be analogues of SP-B and SP-C. However, the surface activity of all these preparations has still to be optimised to be comparable to the behaviour of entirely native natural surfactants. The major challenge for biophysicists is to investigate why the clinical surfactants in use today are so much less effective than native preparations, specially in the presence of surfactant inhibitors, and to develop new synthetic preparations with improved efficacy. To date one of the major difficulties in addressing this issue has been to compare the surface activity of natural and synthetic surfactants, both from a qualitative and a quantitative point of view. Our group has developed novel standardised in-vitro assays that allow accurate evaluation of surfactant activities of different preparations and their comparison with native surfactant materials purified from animal lungs. Results obtained using these methods have allowed us to propose a working model for the molecular events involved in surfactant activity.

### Optimal surfactant activity

The transfer of surfactant lipid/protein complexes from the aqueous layer lining the alveoli to the air–liquid interface involves three important steps:

- transport to the surface
- attachment to the interfacial preformed film
- interfacial molecular transference.

As discussed previously, a surfactant must have good compressibility during expiration and rapid interfacial adsorption during inspiration. In addition, and most importantly, it must also be resistant to inhibition by compounds released into the alveolar spaces during acute lung injury<sup>[9]</sup> (Figure 2). When analysing the surface activity of surfactant preparations, it is not enough to measure compressibility and interfacial adsorption. We need also to determine activity in the presence of inhibitors. In acute lung injury some components are released into the alveolar spaces and somehow become associated with the surface-active film, inactivating the surfactant<sup>[10,11]</sup>. A good therapeutic surfactant must therefore be resistant to inhibition by such compounds. When we measured spreading at the interface of surfactants in the presence or absence of inhibitors (principally plasma components) we found major differences between native surfactant and the natural clinical preparations. Native surfactant and the natural surfactant poractant alfa, for instance, have similar curves in the absence of inhibitors. In the presence of inhibitors, however, whole native surfactant isolated from animal lungs was considerably more resistant to inhibition than all the assayed clinical formulations. These results indicate that further improvement of the structure and composition is required to produce optimised surfactant preparations, with resistance to inhibition at least comparable to that of native surfactant, and potentially useful to rescue respiratory function from acute lung injury.



### Acknowledgments

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# The INSURE approach: does nCPAP and surfactant work only for Vikings?

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## Optimal timing of surfactant treatment

It has long been known that surfactant therapy is effective in improving the immediate need for respiratory support and the clinical outcome in preterm infants, but the optimal timing of surfactant administration is still unclear. This subject has been the focus of two recent systematic reviews. The first compared the use of prophylactic vs. rescue surfactant in infants at risk for RDS and the second compared early vs. delayed selective surfactant treatment for neonatal RDS<sup>[1,2]</sup>.

## Prophylactic surfactant improves clinical outcome

Prophylactic administration of surfactant to infants at risk of developing RDS (<30–32 weeks GA) compared with the selective use of surfactants in infants with established RDS, improves clinical outcome<sup>[1]</sup>. Infants who receive prophylactic surfactant have a decreased risk of PTX, PIE and mortality. What is not yet clear is how to define patients at risk.

## Early surfactant use recommended

Early selective administration of surfactant therapy to infants with RDS requiring assisted ventilation reduces the risk of pulmonary injury (PTX, PIE), neonatal mortality and CLD, compared to delaying treatment in such infants until they have established RDS<sup>[2]</sup>. Early treatment with surfactant in infants at risk is recommended.

## Mechanical ventilation: friend or foe?

Management of VLBW infants varies substantially from hospital to hospital, with diverse management strategies leading to significant differences in the incidence of CLD. MV for preterm infants has long been recognised to contribute to lung injury and, despite surfactant replacement therapy, BPD and CLD continue to be clinically important complications of preterm birth and MV. A recent observational study comparing the prevalence of CLD in a series of large NICUs, identified initiation of MV as the major risk factor associated with an increased risk of CLD among VLBW infants. When management strategies were compared, most of the increased risk of CLD (4 vs. 22%) was explained by the initiation of MV (29 vs. 75%)<sup>[3]</sup>. The NICU with one of the best clinical outcomes and the lowest incidence of CLD also had the lowest rate of MV.

## Surfactant reduces need for mechanical ventilation

In the era of surfactant replacement treatment, a number of workers investigated if instillation of surfactant alone to infants with RDS on nCPAP could reduce the need for MV. In one study in infants with moderate-to-severe RDS treated with nCPAP, a single dose of surfactant significantly reduced the need for subsequent MV (43% vs. 85%



for surfactant plus nCPAP and nCPAP alone)<sup>[4]</sup>. Furthermore, early (at randomisation when  $a/APO_2 < 0.36$ ) compared with late (when  $a/APO_2 < 0.22$  for 30 minutes) treatment with surfactant reduced MV/death both at 0–7 days (21% vs. 63%) and before discharge (25% vs. 68%)<sup>[5]</sup>.

## The INSURE approach

Since the late 1960s continuous distending airway pressure has been used in the treatment of HMD in preterm infants, but in most NICUs MV has now replaced this method. Initiation of MV is known to be associated with an increased risk of CLD and this, together with the fact that in Scandinavia the use of nCPAP remains the basic intervention for VLBW infants with HMD, led us to investigate whether a strategy of nCPAP in combination with surfactant administration during a short intubation (INTubation-SURfactant-Extubation: INSURE) could reduce the number of preterm infants requiring MV.

The trial was conducted in hospitals in the Stockholm region (annual birth rate 24,000). When the study began in 1998, a total of three Level II units and one Level III unit with nine intensive care cots served the region. Intrauterine transfers were carried out for all pregnancies <27 weeks and all preterm infants were taken to the regional Level III unit for ventilation when necessary. Infants of >27 weeks GA with RDS were intubated and received 100 mg/kg poractant alfa when their  $a/APO_2$  was  $\leq 0.22$  ( $FiO_2$  approx. 0.45). They were then extubated immediately after administration, with the time between induction of analgesia and extubation around 4–8 minutes. The main efficacy variable was the need for postnatal transfer to the Level III unit, and infants requiring MV during their first week of life were considered to be treatment failures.

In total 131 babies were born with RDS at GA  $\geq 27$  and <34 weeks during the period 1998–2000 (71 Level III and 60 Level II) (Table 1). Of these, 30 with a mean GA of 28.6 weeks (BW 1300 g) were treated at a Level II unit with the INSURE procedure. The mean postnatal age at treatment was 18 hours. Treatment increased  $a/APO_2$  from 0.20 to 0.50 (corresponding  $FiO_2$ : 0.59 and 0.32) one hour after treatment and remained approximately at this level for the next 48 hours (Figure 1). All babies survived the procedure and only six deteriorated following INSURE and subsequently required MV. During the period 1998–2001, 15 infants required transfer to the Level III unit compared with 47 during the preceding three years.

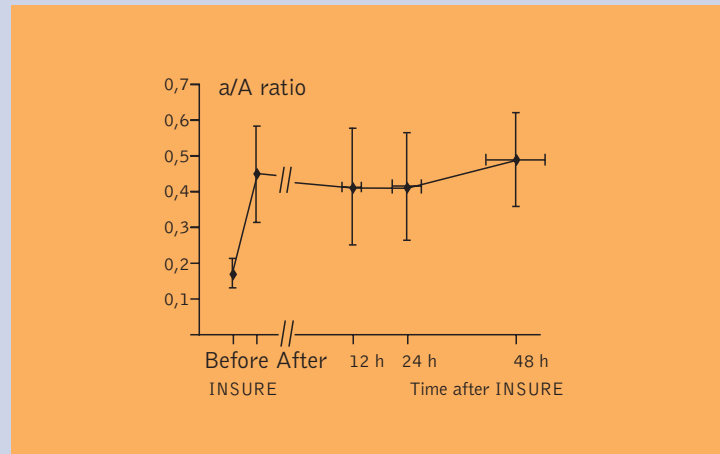
**Table 1.** Preterm infants ( $\geq 27$  weeks and < 34 weeks) with respiratory distress syndrome born in hospitals in the greater Stockholm region during the period 1998–2000 (n=131)

	Tertiary care (n=71)	Level II (n=60)	
GA	30	29.3	n.s.
BW	1826	1397	n.s.
RDS	71	60	n.s.
Surfactant	42 (60%)	42 (70%)	n.s.
INSURE	0	30(50%)	
Respirator	42 (60%)	12 (20%)	< 0.001
CLD	6 (9%)	3 (5%)	n.s.
IVH any grade	2 (2.8%)	1 (1.7%)	n.s.
ROP, treated	0	0	

## INSURE: does it work only for Vikings?

Results of two recently presented studies indicate that these encouraging results are not peculiar to our study group but are reproduced in other patient populations. In the Vermont-Oxford network trial, spontaneously breathing infants treated with early intubation, surfactant replacement, and rapid extubation were less likely to require MV during the first week of life than infants who received selective treatment<sup>[6]</sup>. In the Rochester study, which involved 105 infants (29.0–35.9 weeks GA) with RDS requiring nCPAP, transient intubation solely for the administration of surfactant was effective in reducing later intubation for MV<sup>[7]</sup>. The authors suggested that this approach might decrease the need for invasive, expensive treatments for RDS, particularly in areas where resources are limited.

Figure 1. a/APO<sub>2</sub> ratio in preterm infants (mean GA 28.6) at 48 hours following treatment with INSURE.



## Conclusions

- Combined use of early nCPAP and instillation of rescue surfactant reduces the need for MV.
- This strategy has important implications for the choice of treatment, its costs and the increasing requirement for family-centred neonatal care.

In our hands, nCPAP with INSURE reduces the need for MV in preterm infants with a parallel reduction in the need for postnatal transfers to our tertiary care centres. It should be remembered that these infants still require close surveillance and monitoring and that experience in good nCPAP technique and care of VLBW infants is mandatory. Results from the Vermont-Oxford Network and the Rochester trials add additional weight to our results and put them in an international perspective.

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## CPAP and prophylactic surfactant

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### Preterm birth and mechanical ventilation disrupt lung development

Prematurity, a common cause of neonatal death is also often associated with serious complications in babies who survive. Preterm birth and subsequent ventilation disrupt the normal sequence of lung development leading to

chronic/acute lung disease. Around 60% of infants born at <30 weeks GA will be affected by RDS, a deficiency of surfactant that results in poor lung compliance and increased work of breathing. When the lungs are depleted of surfactant a vicious circle is set in motion. The alveoli collapse, the lungs become stiff, compliance falls, FRC is decreased and dead space and work of breathing are increased. Epithelial damage caused by gasping sets up a cytokine-mediated inflammatory response leading to severe hypoxia, respiratory acidosis, and surfactant inhibition (Figure 1). Extremely preterm babies with RDS are at risk of developing BPD, however so are those with little initial lung disease. Multiple factors before and after birth interact to produce BPD.

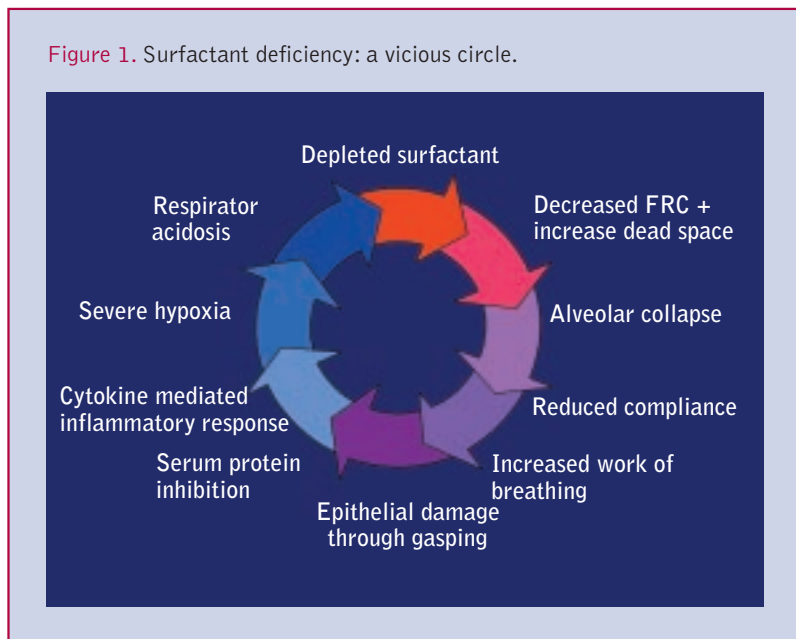
Factors including intrauterine cytokine exposure, initiation of ventilation, continued ventilation and postnatal infection interact to cause lung injury/inflammation, with resulting inhibition of alveolarisation and associated dysmorphic vascular development. We now know that damage occurs from the outset with:

- resuscitation
- ventilation
- or even simply spontaneous breathing when the lung is surfactant deficient.

Allowing breathing in the immature lung is to allow harm to that lung, which may or may not be recoverable. We cannot prevent breathing so how can we prevent this damage from occurring?

### nCPAP and surfactant therapy

It has long been recognised that nCPAP, a less invasive method of respiratory support than intubation, can reduce the need for MV. nCPAP improves oxygenation (without deleterious effects on PaCO<sub>2</sub> or blood pressure) through



initial stabilisation of alveoli and then gradual expansion of collapsed alveoli. FRC is therefore increased with a resulting increase in alveolar surface area for gas exchange and decreased intrapulmonary shunting. nCPAP also conserves pulmonary surfactant. In addition, the baby should experience a decrease in respiratory rate, regularisation of the breathing pattern, and decreased work of breathing.

In view of the properties and activities of nCPAP and surfactant it seems reasonable to assume that a combination of the two could play a role in the management of preterm infants (Table 1). Almost a decade ago preliminary work by Verder et al. showed that, in neonates with moderate-to-severe RDS treated initially with nCPAP, a single dose of poractant alfa (Curosurf®, Chiesi Farmaceutici) markedly reduced the need for MV<sup>[1]</sup>. A subsequent trial showed that earlier treatment with surfactant (median 5.2 hours of age) significantly lowered the need for MV in preterm infants supported by nCPAP when compared with late treatment (median 9.9 hours of age)<sup>[2]</sup>.

Table 1. Effects of surfactant alone and in combination with nCPAP

Surfactant alone	Surfactant in combination with nCPAP
<ul style="list-style-type: none"> <li>• Lowers surface tension</li> <li>• Prevents alveoli collapsing at end of expiration</li> <li>• Prevents alveolar disruption during breathing or ventilation</li> <li>• Acts as a barrier to proteinaceous exudate</li> <li>• Helps protect the lung from bacteria</li> <li>• Has high anti-oxidant activity and anti-inflammatory effects</li> <li>• Down regulates the cytokine system and reduces neutrophil chemotaxis</li> </ul>	<ul style="list-style-type: none"> <li>• Minimises volutrauma — ventilation primary risk factor for BPD</li> <li>• Intervenes to prevent atelectasis and the ongoing cascade leading to lung injury</li> <li>• Reduces lung inflammation</li> <li>• Removes a port of access for infection</li> </ul>

## nCPAP and prophylactic natural surfactant

These data demonstrate the efficacy of the combination in reducing the need for MV, but what happens if we give surfactant prophylactically? A large-scale trial conducted by the IFDAS study group in the UK was designed to test the hypothesis that combining prophylactic surfactant (poractant alfa) with early nCPAP (Infant Flow™) would reduce the need for MV. The rationale for the study was that nCPAP is minimally invasive and can assist in the establishment a FRC without risk of over distension. When combined with prophylactic natural surfactant, the early lowering of surface tension at the time FRC is being established would further improve the baby's respiratory condition preventing the need for MV. Natural surfactant when given prophylactically has been shown to result in the greatest reduction of mortality and pulmonary air leakage<sup>[3]</sup>. Poractant alfa has also been shown to reduce the incidence of BPD in infants of <30 weeks GA<sup>[4]</sup>.

### IFDAS results

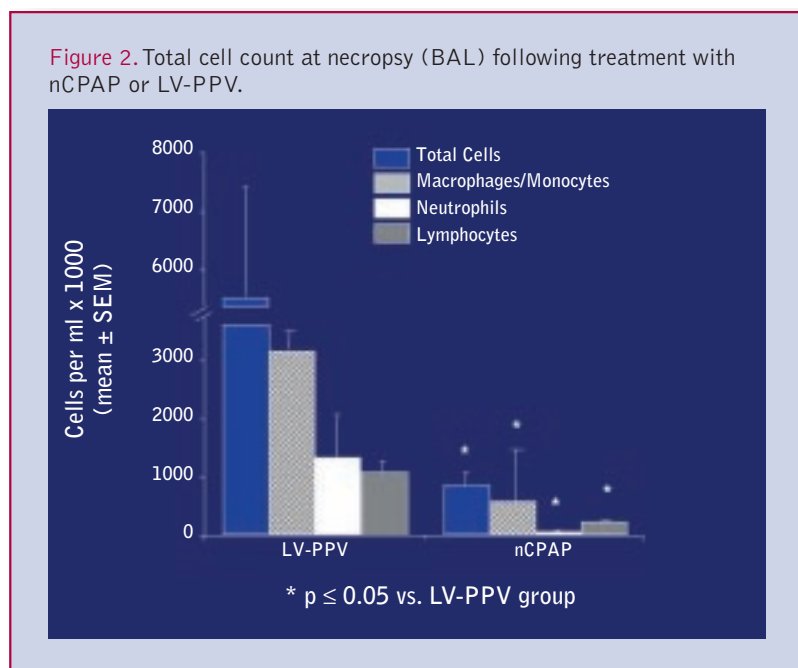
In a prospective multicentre trial, 237 inborn infants with a GA of 27–29 weeks were randomised before birth to one of four treatment arms: early nCPAP with prophylactic surfactant (group 1), early nCPAP ± rescue surfactant (group 2), early IPPV with prophylactic surfactant (group 3), and conventional management (IPPV ± rescue surfactant) (group 4). Prophylactic surfactant was administered before 15 minutes of age in groups 1 and 3. In babies randomised to group 1 the aim was to extubate on to nCPAP by 2 hours of age. Similarly any baby who required intubation at or soon after birth in group 2, extubation on to nCPAP by 2 hours of age was the goal. The mothers of 98% of babies had received antenatal steroids; 78% were born more than 24 hours after the administration of the first dose.

The results of the IFDAS trial are encouraging. Importantly, nCPAP alone or in combination with poractant alfa appears to be safe. nCPAP with prophylactic surfactant (group 1), or nCPAP alone (group 2) reduced the need for MV in the first 5 days of life ( $P < 0.001$ ). nCPAP with prophylactic surfactant had a beneficial effect in babies with a GA of  $< 29$  weeks when combining the two treatments resulted in a greater reduction in short term ventilation than nCPAP alone. The combination of prophylactic surfactant with nCPAP (group 1) resulted in the need for fewer repeat doses of surfactant than did any of the other three treatment groups ( $P < 0.005$ ). No strategy reduced total duration of respiratory support or reduced oxygen dependency at 28 days or 36 weeks. The trial was not powered to show an effect on BPD so it is not surprising that it failed to do so. However, it did show that it is possible to safely manage these babies with nCPAP and that for those infants  $< 29$  weeks GA the combination of prophylactic surfactant with nCPAP was helpful in preventing the need for MV in the initial few days of life, which is thought to be a critical period for lung injury. The key question ‘Does nCPAP in combination with a prophylactic surfactant reduce lung damage?’ remains unanswered. It could be that multicentre, randomised trials will not provide an answer. BPD is a complex multifactorial disease therefore very large trials will be required to test the possible effect of any treatment. An animal model may help provide the missing data.

### Animal model for BPD

The 125-day baboon has lung development equivalent to 25 weeks human gestation; the lungs are in the late canalicular stage of development. This model has proved to be extremely helpful to our understanding of the evolution of BPD. We are currently evaluating the effect of prophylactic surfactant combined with early nCPAP in this model. The dam receives antenatal steroids 24 and 48 hours before caesarean section. Poractant alfa (200 mg/kg) is administered before the first mechanical breath. The animal receives LV-PPV with poractant alfa repeated (100 mg/kg) at 6 hours. Extubation to nCPAP is possible at 24 hours once the effect of maternal sedation has worn off. Lung morphometry is carried out at 28 days.

Clinical results demonstrate that animals treated with prophylactic surfactant and early nCPAP are less ill, need less respiratory support and have better respiratory physiology. At necropsy, the lungs show no sign of infection. The saccules/alveoli have thin walls and are evenly inflated with appropriate vascular development in contrast to those of ventilated animals where the characteristic appearances of BPD are seen<sup>[5]</sup>. Importantly there is less evidence of inflammation (Figure 2).



Following the positive results obtained with this initial work, questions still remain unanswered. These include:

- Does lung development in the nCPAP model parallel that which occurs *in utero*? (Comparison with appropriate gestational control.)
- What happens if ventilation is just for a few days before extubation to nCPAP? (Are the lungs damaged to the same degree as in the previous model where ventilation was for several weeks<sup>[5]</sup>?)
- Is the preservation of lung development seen in the 28-day nCPAP model continued in infancy and beyond?

Preliminary results from ongoing studies are encouraging. Data indicate that early nCPAP combined with prophylactic surfactant enables lung development in this extremely preterm model to progress in a very similar manner to that which occurs *in utero*. It remains to be seen if this preservation continues into infancy and adult life.

## Conclusions

We believe that preterm birth and subsequent ventilation disrupt the sequence of normal lung development. It is therefore vital that we develop strategies that will safely and effectively help prevent lung damage in preterm infants. It is important therefore that we base such a strategy on the progressive changes in structure and vulnerabilities to injury that occur in the lungs as GA advances. Our recommended strategy very much depends on the stage of lung development (*Table 2*). In infants with a GA of <28 weeks prophylactic surfactant and nCPAP is recommended, while in those with a GA of 30 weeks and above, rescue nCPAP and surfactant is the treatment of choice. The situation is less clear-cut in infants in the intermediate group (28–29 weeks) however prophylactic surfactant and nCPAP and INSURE appear to be the treatments to consider.

**Table 2.** Recommended strategy for management of respiratory problems in preterm infants

Stage of lung development	Recommended intervention
<28 weeks <ul style="list-style-type: none"> <li>Lung is at very vulnerable canalicular stage of development</li> </ul>	Prophylactic surfactant and nCPAP
28–29 weeks <ul style="list-style-type: none"> <li>Lung may still be vulnerable</li> <li>Early saccular/alveoli and associated vascular development</li> </ul>	Prophylactic surfactant and nCPAP or INSURE
30 weeks and above <ul style="list-style-type: none"> <li>Secondary crests, elastin and vasculature structure developed</li> </ul>	Rescue nCPAP and surfactant

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## Concluding remarks

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### Surfactant state of the art and future developments

The aim of this symposium was to try to develop a protocol for surfactant treatment. Exciting new data were presented here today.

The main topics covered were:

- Type of surfactant — natural, synthetic and new generation agents**  
 Evidence from clinical trials presented here and from the literature certainly favours the use of natural surfactants rather than synthetic products for the treatment of RDS<sup>[1,2]</sup>. Newer generation surfactant preparations may have a role to play in treating other respiratory disorders if they can be shown to be more resistant to inactivation. There are some preliminary data indicating that increasing the amount of phospholipids in natural surfactants may overcome inactivation but this remains to be confirmed.
- Timing of surfactant treatment — prophylaxis, early or late treatment**  
 Evidence favours prophylaxis for infants of  $\leq 31$  weeks<sup>[3,4]</sup> and early treatment for others.
- Dose of surfactant — 100 mg/kg or 200 mg/kg**  
 The recommended dosage may well depend on the timing of administration (prophylaxis, early or late treatment) and the rate of prenatal steroid use.

### Evidence-based surfactant therapy

Results of the Vermont-Oxford trial of a multifaceted intervention to promote evidence-based surfactant therapy, provide data from 114 hospitals on surfactant use<sup>[5]</sup>. The intervention was successful in reducing the time to first surfactant treatment from 78 to 21 minutes with more than half of infants receiving surfactant in the delivery room compared with 18% of controls. While there was no difference in survival rates, overall there were significant reductions in IVH (all grades) and severe IVH (grades 3 and 4), providing another reason for using surfactant prophylactically or early (*Table 1*). A reduction in severe IVH has already been shown when poractant alfa (Curosurf®, Chiesi Farmaceutici) is given prophylactically rather than as a later treatment<sup>[6]</sup>.

**Table 1.** Summary of results of Vermont–Oxford trial

	Intervention	Control
Time to first dose (minutes)	21	78*
Surfactant use in delivery room (%)	55	18*
IVH (%)	28	33**
Severe IVH	10	14*
** P<0.001, * P<0.05		



## Recommended protocol for surfactant use

Evidence presented here and results of recent trials allow us to recommend a protocol for surfactant use depending on GA. In infants with a GA of <27–28 weeks, prophylaxis with a natural surfactant (100 mg/kg) is recommended. In those of 29–31 weeks GA, early nCPAP with early rescue with natural surfactant (100 mg/kg) is the recommended treatment of choice, while observation is advised initially in those  $\geq 32$  weeks GA with surfactant treatment when more than 40% oxygen is needed (*Table 2*).

**Table 2.** Recommended protocol for surfactant use

GA <27–28 weeks	GA 29–31 weeks	GA $\geq 32$ weeks
Prophylaxis in delivery room (100 mg/kg)	Early nCPAP	Observe
Extubate to nCPAP (usually possible in babies >24 weeks)	Early rescue with 100 mg/kg if $\text{FiO}_2 > 0.30 \pm$ white chest X-ray	Rescue with 100–200 mg/kg if $\text{FiO}_2 > 0.40 \pm$ white chest X-ray

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