It was 1959 when M.E. Avery et al. described for the first time that in the lung of immature babies died of Hyaline Membrane Disease (HMD) there was high surface tension, and theorised that in these cases a surface-active substance was lacking [1].

On August 9th, 1963, Patrick Bouvier Kennedy, the son of USA President John F. Kennedy and Jacqueline Bouvier, died after 39 hours of life, being born 5 ½ weeks premature. This was not a so severe prematurity, but anyhow he was affected by HMD, and at that time only oxygen was available for neonates with respiratory failure. Of course such death gave a great prompt to the research in this field.

As M.E. Avery herself reports, the presence of a surface-active agent within the lungs was still a topic for few pulmonary physiologists till the development from Clements of the Bubble Stability Test (BST)[2], a test that made easy to measure in an indirect way the amniotic fluid content of phospholipids. The BST is very simple to perform: adding normal saline in growing quantity in 5 tubes with a modest quantity of amniotic fluid then added up with ethanol and vigorously shaken creates a ring of bubbles over the fluid. If three of these rings remain stable after 15 minutes, then it indicates that the lung is mature, i.e. the lecithin to sphingomyelin ratio (L/S) of amniotic fluid is mature or >2. Still nowadays the more precise thin layer chromatographic L/S test is not available everywhere and is time consuming, with the answer arriving mostly after the baby is born. Therefore, given its simplicity and its clinical application in the timing of the delivery, the BST gave a new impulse to research on HMD.

At almost the same time, the prevention of HMD by antenatal administration to the pregnant woman of steroids was proposed [3]. This was another milestone in the history of neonatal HMD: the administration of antenatal steroids could reduce the incidence and the severity of HMD in the premature infant, by speeding up its pulmonary maturation. Antenatal steroids, besides, reduced the risk of intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), hyperbilirubinemia and also death [4]. Even with such good perspectives, use of steroids – basically betamethasone and dexamethasone given twice in 24 hours one week before delivery – in premature pregnancy is not yet uniform between centres, some having percentage as high as 97% and others as low as 30%. Indeed steroids can provoke problems in the pregnant woman such as fluid retention, altered glycemic control, hypertension, pulmonary oedema and increased risk of sepsis. Various undesired collateral effects have been described also in the foetus and the neonate: foetal growth restriction after multiple courses, suppression of the foetal pituitary-adrenal axis, transient hypertrophic cardiomyopathy [5-9].

Between the end of ‘70s and the first ‘80s eventually arrived the preparation that all were awaiting: if in the lungs of babies with HMD the quantity of surface-active agent, that we can now call surfactant (SF), is low and this is the basis of the disease, one could obtain SF from the lungs of animals or try to synthesise an equivalent and give it to the infant, directly in the lung, to replace
the lacking of the natural one. Therefore several preparations of exogenous SF were proposed and tested since then.

**Keywords:** Neonatal Respiratory Distress Syndrome; Hyaline Membrane Disease; Surfactant; Surfactant Associated Protein; Mortality; Pneumothorax; Antenatal Steroids

**Abbreviations:**

ARDS: Adult Respiratory Distress Syndrome; BPD: Bronchopulmonary Dysplasia; BST: Bubble Stability Test; DPPC: Dipalmitoylphosphatidylcoline; HMD: Hyaline Membrane Disease; IVH: Intraventricular haemorrhage; L/S: Lecithin to sphingomyelin ratio (L/S); MAS: Meconium Aspiration Syndrome; n-CPAP: nasal continuous positive airway pressure; NEC: Necrotising enterocolitis; NRDS: Neonatal Respiratory Distress Syndrome; PC: Phosphatidylcoline; PG: Phosphatidylglycerol; PPHN: Persistent pulmonary hypertension of the neonate; PTX: Pneumothorax; RCT: Randomised controlled trial; SF: Surfactant; SP: Surfactant associated protein; TM: Tubular myelin

**Exogenous Surfactant preparations**

Pulmonary SF in nature is a lipoprotein essentially constituted by phospholipids and mainly by dipalmitoylphosphatidylcoline (DPPC), phosphatidylcoline (PC), phosphatidylglycerol (PG) plus at least 4 surfactant-associated proteins (SP): SP-A, SP-B, SP-C, SP-D. These last account for about 5% of SF composition.

SFs at the beginnings were prepared by extraction from lungs of rabbit, calf, pig, and also from human amniotic fluid, with some difference one another but all containing SPs. One of the main function of SPs is to facilitate spreading and function of SF. Also synthetic protein-free SFs were prepared, composed mainly by DPPC ± other phospholipids and non-proteic spreading agents to mimick SPs action (see table).

SP-A, a glycoprotein of the category of collectin, is the basis of the reserve of SF in the hypophase, in the alveoli. It is necessary to constitute Tubular myelin (TM), i.e. a sort of net with SF that is rapidly available in case of need. The molecular weight of SP-A is 28-36 kDa.

SP-B and SP-C, two hydrophobic amphipilic proteins, are instead essential components of SF itself, allowing its distribution as a monolayer at the interface and at the same moment making possible its folding during expiration, when the alveolar volume reduces. The molecular weight of SP-B is 8 kDa while that of SP-C is 42. kDa. Both these smaller proteins are produced in the type II pneumocytes as is SF itself. Reserves of SF are accumulated within type II pneumocytes as lamellar bodies and are secreted in the hypophase when needed: e.g. close to the delivery. The relative increased number of areas with high concentration of DPPC, that has a more rigid structure compared to other phospholipids, allows SF to create a sort of biochemical skeleton of the alveolus that do not collapse during expiration. This in turn creates a residual volume and a functional residual capacity that, for the Laplace’s law, permits that the next inspiration requires lower driving pressure, therefore reducing the work of breathing. When SF lacks, the alveoli tend to collapse at the end of expiration and the strength requested to open them again is very high. The difficulty to open the lungs is the basis of neonatal respiratory distress syndrome (NRDS) that is followed by hypoxia, acidosis, damage to type II pneumocytes, presence of SF-inhibiting plasma proteins in the alveoli, intractable respiratory failure. Indeed, the acronym NRDS that identify the clinical entity of the problem, took the place of HMD that remained a post-mortem examination definition due to the presence of eosinophil – i.e. hyaline – membranes in the alveoli of the babies died of NRDS. This was also an effect of the marked improved survival of such babies after the advent of exogenous SFs, with the need of doing a clinical diagnosis consistent with autopic HMD. Deficiency of SP-B seems more important than that of SP-C to develop RDS; in fact genetically lacking SP-B animals and humans develop intractable and lethal RDS that, in the less severe surviving cases can be resolved only by lung transplant, while the genetic deficiency of SP-C allows survival but facilitate the development of interstitial chronic lung disease.

SP-D is a collectin, a protein that probably has mainly immune functions [10-13].

**Natural or artificial SF for rescue treatment of RDS**

A first important split in the identification of SFs was therefore the presence or not in it of SPs.

First experimental studies identified that both SFs with SPs and the protein-free ones had effects on NRDS of immature animals in laboratory, and at the same time a concept began to develop: SF had to be administered as soon as possible to avoid pulmonary necrosis [14].

Morley showed that the administration of a pharyngeal dose of a synthetic surfactant preparation (ALEC® = Artificial Lung Expanding Compound) associated with 3 other doses of ALEC® via endotracheal tube was able to reduce mortality and complications in <30 wks’ gestation premature infants [15].
Another protein-free artificial SF, Exosurf®, was widely diffused in the late 80’s and first 90’s, and a very great collaborative multicenter study on 6774 infants reported that its administration as a preventive measure in the first 2 hours of life (early administration) could reduce pneumothorax (PTX) and need of supplementary oxygen at expected date of delivery versus those who received Exosurf® in a tardy way [16]. However, in the same time, many other randomized controlled trials (RCT) showed that SFs derived from animals, in particular calf and porcine derived SFs, were as effective as synthetic SFs but their effect on gas exchange was much more rapid, within minutes from endotracheal administration [17-20]. A recently updated review compared 15 randomized clinical trials of natural SFs vs those of protein-free synthetic SFs for NRDS and found out that use of natural SFs significantly reduced the risk of PTX and, at a lesser extent, the mortality and the risk of developing bronchopulmonary dysplasia (BPD) vs the protein-free SFs. However protein-free SFs scored better concerning the development of necrotising enterocolitis (NEC) and grade 1-2 intraventricular haemorrhage (IVH). As regards respiratory care, the babies treated with natural SFs showed greater early improvement in the ventilator requirements. The study concluded that even if there was not a great difference in general outcome, natural SFs are preferable vs the nowadays available protein-free SFs [21]. The protein-free SFs are nowadays out of marketing in various countries. The human SF, even if presented a lower risk of sensitisation, was withdrawn from the market mainly because too difficult to be produced: 1 dose required the amniotic liquid of 3 term pregnancies. Therefore the next parts concerning the use of SF will be dedicated to natural animal SFs.

### Early vs late administration

Since the beginning SF was used for clinically severe NRDS, i.e. those requiring mechanical ventilation and ≥ 60% supple-

<table>
<thead>
<tr>
<th>Type of surfactant</th>
<th>Preparation</th>
<th>Name</th>
<th>Protein</th>
<th>Content of phospholipids (mg/ml)</th>
<th>Usual dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>Minced lung extracts</td>
<td>Surfactant TA (Surfacten®)</td>
<td>SP-B &amp; SP-C</td>
<td>30</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beractant (Survanta®)</td>
<td>SP-B &amp; SP-C</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poractant-α (Curosurf®)</td>
<td>SP-B &amp; SP-C</td>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Lung lavage extracts</td>
<td>Bovine Lipid Extract Surfactant (BLES®)</td>
<td>SP-B &amp; SP-C</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calfactant (Infasurf®)</td>
<td>SP-B &amp; SP-C</td>
<td>35</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SF-RIT (Alveofact®)</td>
<td>SP-B &amp; SP-C</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Amniotic fluid extract</td>
<td>Human surfactant</td>
<td>SP-B &amp; SP-C</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>Synthetic</td>
<td>Protein-free</td>
<td>Pumactant (ALEC®)</td>
<td>none</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collosceril palmitate (Exosurf®)</td>
<td>none</td>
<td>13.5</td>
<td>67.5</td>
</tr>
<tr>
<td></td>
<td>Containing protein analogues</td>
<td>Lucinactant (Surfaxin®)</td>
<td>Analogue SP-B</td>
<td>30</td>
<td>175</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rSP-C surfactant (Venticute®)</td>
<td>Analogue SP-C</td>
<td>50</td>
<td>50*</td>
</tr>
</tbody>
</table>

* in ARDS

**Table - Characteristics of different surfactant preparations.**
mental oxygen. Its effect was very rapid, but often complicating diseases could not be avoided, as IVH, NEC, pneumonia, haemodynamically significant patency of ductus arteriosus (PDA), BPD, to say the most frequently encountered of them. From the previous animal studies and the results of the clinical trials it was theorised that an early administration could improve outcome vs a delayed one. Early could signify “early as time” i.e. within a time-range from birth or “early in the course of the disease” i.e. when the requirement of oxygen was lower in the early vs the late group. Studies could show that an early treatment “as time” was advantageous over a tardy treatment, but especially that an early treatment “in the course of the disease” could not only reduce the complications, but also halt the progression of the disease.

Besides a slight reduction of the cost of hospital care was also reported with the early strategy surfactant treatment [22-25].

Prophylaxis

Prevention of NRDS is the target of neonatologists as well of obstetricians. While the only antenatal preventive measure was the administration of steroids to the pregnant woman, however it was quickly clear that steroids couldn’t eliminate NRDS both because not so diffuse and because had possible undesired side effects, in particular hyperglycemia in the diabetic mother, hypertension in the mother with pregnancy induced hypertension, restriction of growth, restriction of growth for more than one course of two 12 hours apart administrations.

Therefore RCTs were conducted, especially in babies less than 30 wks’ gestation, i.e. those babies that had high probability of requiring resuscitation manouvers at birth, including intubation. Results were very good and babies given prophylaxis had a better outcome both for the subsequent development or not of NRDS and the lower percentage of PTX and reduced mortality [26-33]. However larger studies done more recently and taking into account the actual more diffuse use of antenatal steroids and the use of lung stabilisation with nasal-continuous positive airway pressure (n-CPAP) already in the delivery room, found out that early stabilization with n-CPAP and selective SF administration only to the patients requiring intubation was superior to intubation and administration of SF to all very preterm infants in reducing risk of chronic lung disease or death [34].

High vs low dose

Different SFs has different concentration of phospholipids, with poractant-α having the highest concentration, i.e. 80 mg/ml and the possibility of administering a quantity of 200 mg/kg phospholipids as a bolus dose in 2.5 ml. Other SFs have a lower concentration and therefore require higher volumes to be distributed. However also the quality and percentage of SPs account for the quality of SF, and some present higher resistance to inactivation by phospholipase or substances like blood and meconium.

The best dose is, of course, that allowing to administer SF only once; in fact the procedure of administration, albeit life-saving, is a destabilising manouver for the baby, even if it gives benefits. Few side-effects during administration – apnea, bradycardia, cyanosis – have been reported in the RCTs, and they are principally due to vagal stimulation and/or flooding of the lungs, but also to the viscous properties of SF at body temperature. Therefore, because the better spreading of SF is by bolus injection within the endotracheal tube, the most of undesired side effects of administration seem related to the volume of SF and to SF properties because it can precipitate and form intrabronchial plugs. For SFs with higher volume/dose ratio, the partition of the dose in 2 – 3 – 4 aliquotes delivered in close sequence and in different position of the baby is an advice given by some pharmaceutical brands to improve distribution, but probably aimed to reduce side effects too.

In any case the major question posed by RCTs was if 200 mg/kg was better than 100 mg/kg. In particular there were 2 types of studies: poractant-α 200 mg/kg vs poractant-α 100 mg/kg and bovine SF against poractant-α. A comparative analysis of such studies pointed out how 200 mg/kg poractant-α (a porcine SF) could improve mortality and pulmonary complications in NRDS vs bovine SF, while bovine SF at the dosage of 100 mg/kg, could improve cerebral perfusion at a faster rate than poractant-α [35-39].

A practical problem is which is the optimal dose of SF for NRDS. From clinical trials one can derive that 200 mg/kg for poractant-α and 100 mg/kg for the available bovine SFs is the optimal first dose, and multiple doses will be halved. However what does happen in the clinical setting, and especially in the delivery room – where the weight of the infant is estimated –, is that vials are used entirely, due to the high cost. To give an example a baby weighing 1300 gr can receive a lower dose of SF (240 mg of poractant-α instead of 260 mg or 100 mg of beractant instead of 130 mg) while an 850 gr infant can receive a higher dose (240 mg of poractant-α instead of 170 mg or 100 mg of beractant instead of 85 mg). As a consequence also results can change and this should be kept in mind.

Multiple doses: another question to which answer

If one dose is not enough, are multiple doses better? In studies of natural SFs multiple doses were associated with significant decrease in mortality and risk of PTX. Results from protein-free SFs are not reported because the most of them are not anymore available on the market [40,41].

Therefore it seems that to give more doses of natural SF improves outcome, even if a cost/benefit analysis is not available.
Oxidative stress

One early concern was if the impressiverapidity of improvement, especially of oxygenation, could create oxidative stress with the related undesired effecct to ease the development of inflammation, BPD, IVH and retinopathy of prematurity. Even if such diseases did not appear increased in the RCTs however no study reported a reduced incidence of BPD in survivors and only the mortality or BPD index could be reduced. This means that SF alone wouldn’t be able to reduce incidence of BPD and that other factors have to be analysed, that are different from prematurity itself.

Few and limited studies reported measurement of oxidative stress after SF administration. One study reported increase of total antioxidative capacity after SF administration, implying an activation of antioxidant defenses. Another could record a non-significant increase of oxidative stress, measured as increase of reactive oxygen species after SF instillation. Two points must be kept in mind for these studies: i) the number of cases was limited, and ii) supplementary oxygen was rapidly reduced by protocol - as soon as transcutaneous oxygen saturation improved – minimising the oxidative stress and therefore making difficult to evidence any difference between before and after SF administration [42,43].

Synthetic proteins

Use of SF is now widespread, the SFs used are the natural ones, with natural SPs. However there are problems: even if no study evidenced development of allergy, the animal proteins might stimulate it. Besides natural SFs are very expensive and costs of healthcare are always increasing while national public resources are in short supply. Therefore, because SFs are more efficient when tied to SPs, artificial SFs with synthetic SPs have been produced and tested (see table).

In particular analogues of SP-B and SP-C have been added to phospholipids. Analog of SP-B is the 21-residue peptide KLLLLKLLLLKLKLLKLLKLLK called sinapultide or KL4 and has been conjugated with dodecylphosphocholine, DPPC and PG to form the lucinactant.

Analogue of SP-C is the following peptide CPVHLKRLLLLLLLLLLLLLLLLLL that has been conjugated with DPPC, PG and PC and whose properties in vitro were similar to those of SF-TA.

Such synthetic SFs, especially lucinactant, have been studied on neonates and have obtained good results. However problems remain to be resolved: SP-B analogue synthetic SF seems better than SP-C analogue synthetic SF; lucinactant however has a long preparation time and the time for administration is about 15 minutes against 7 minutes of the natural SFs; lucinactant has a low content of phospholipids/ml and therefore requires high volumes of administration and must be divided in more aliquots. Besides the main RCT study of non-inferiority of lucinactant vs poractant-α was interrupted before having reached the foreseen cases because recruitment of cases was going too slowly; however this imply that the results cannot be considered trustworthy.

SP-C analogue synthetic SF was used especially in adults with adult form of respiratory distress and experience on NRDS is experimental, even if promising.

At present however there is no evidence justifying the use of one synthetic SF with protein analogue instead of a natural SF. Studies of a synthetic SF with both SP-B and SP-C analogues to improve lung stabilization are in progress [44-51].

Methods of administration

After the first studies that imposed the administration of SF directly in trachea via the endotracheal tube and that were conducted in already intubated very severe cases, gradually SF was used in infants that had less severe form of NRDS, that were spontaneously breathing and in which it was supposed the administration of SF could have avoided further intubation and mechanical ventilation. The first Danish-Swedish study on such infants could show that premature babies with NRDS treated with n-CPAP took advantage from the administration of SF with the technique called INSURE = Intubation – SURfactant administration – Extubation. Babies received n-CPAP before and after INSURE. This study opened the way to other studies that showed how lung stabilization with n-CPAP at birth was at least as equivalent as SF given at birth by INSURE. Actually, indeed, n-CPAP is the most used technique of lung stabilization at birth in premature infants unless they need to be intubated, in which case SF is given by INSURE and extubation attempted rapidly after SF action, if the baby can sustain spontaneous breathing [52-54].

Of course the INSURE technique is not a non-invasive modality of administration.

Administration via a supraglottic device called laryngeal mask seems possible from limited studies and gives promising results, both vs traditional intubation and INSURE. The actual major limit is the dimension of the smallest masks that can be used with a certain difficulty in babies with birth weight lower than 1500 grams, but would have especially application in greater babies that often requires sedation for intubation [55-58].

Another technique that is presented as mini-invasive is a particular form of INSURE: the baby remains on n-CPAP during all the procedure, is intubated with a small naso-gastric feeding tube that does not occlude the laryngeal lumen allowing the continuous alveolar recruitment given by n-CPAP. SF is in-
jected via such tube, then the patient returns on n-CPAP. This technique is called LISA = less invasive surfactant administration. The invasivity of the technique is not inferior to that of INSURE, but the lung continue to be recruited during the maneuver, theorising a better distribution of SF. Such technique has been studied and, in skilled hands, appears safe and effective [59-61].

However the most awaited method of administration of SF and the less invasive is the nebulisation. In spite of such expectation while studies done on animal promise interesting future development, the few babies treated with nebulized SF + n-CPAP did not show changes vs n-CPAP alone [62,63]. More studies are necessary.

Other uses of SF in infants [64-69]

Pneumonia, especially that caused by Group B Streptococcus that determines a radiological picture that is indistinguishable from that of NRDS, is a disease in which damage to type-II pneumocytes and factors of inflammation determine an inactivation of the available SF, and the impossibility of producing and releasing new SF consequently to type-II pneumocytes damage. The administration of SF is beneficial, but often multiple doses are requested.

Meconium aspiration syndrome (MAS) is due to the inhalation of SF secondary to severe intra-uterine asphyxia. Meconium has high viscosity and tends to occlude airways and alveoli, besides its components highly inhibits alveolar SF both by inactivation and competition. The clinical picture is one of severe respiratory failure, with very difficult to ventilate uneven lung. Administration of SF has been done taking advantage in primis of its detergent properties therefore using it diluted to perform lung lavage, and in secundis as bolus replacement therapy for the SF that was inactivated or washed out with lavage. Use of SF both as lavage or bolus was shown to reduce both duration of mechanical ventilation and hospital stay, and for babies receiving bolus SF, also need of extracorporeal membrane oxygenation.

Pulmonary haemorrhage is the presence of blood within the respiratory spaces of the lungs. There is a mechanical effect of occlusion of the respiratory part of the lung flooded by blood associated with an inhibitory effect of blood on SF and, if massive, also hypovolemic shock. One small RCT reports similar improvement of oxygenation after administration of poractant-α or beractant in very low birth weight infants with pulmonary haemorrhage, and no difference in the rates of BPD and mortality between the two SFs.

Persistent pulmonary hypertension of the neonate (PPHN), rarely a primary disease, is often present as a complication of both pneumonia and MAS. It is due to the persistency of the foetal circulation due to the high resistances in the pulmonary vascular bed. The therapy of PPHN is the use of pulmonary vasodilating drugs, and the first is oxygen. Administration of SF, especially of those rich in SP-B as calfactant and poractant-α, improves alveolar recruitment and oxygenation, and allows specific drugs, as inhaled nitric oxide, better distribution and therefore action. This kind of pre-treatment with SF has contributed to the reduced use of extracorporeal membrane oxygenation for PPHN.

The future

The future possible applications of SF are several: first of all it is necessary to establish an effective non-invasive delivery mode as nebulisation, then it is already under evaluation the possibility of delivering drugs within the lungs conveyed by SF itself, as antibiotics, steroids, anti-oxidants substances, and so on. The possibility of having a synthetic SF with protein analogues at a lower price and with greater resistance to inhibition will certainly give an incentive to the use of SF for children and adults with ARDS, for bronchiolitis and other viral lung disease, for cystic fibrosis, chronic obstructive lung disease, recurrent otitis and as a vehicle for anti-cancer drugs.

Conclusion

In the last 40 years SF has become an impressive reality. Its use has saved thousands of very preterm and full-term infants and also reduced the complications of NRDS. It is now a routine treatment in the intensive care units, but the always less invasive methods of administration open the field to its use in almost all the delivery centres and, to give an example, to the treatment of full-term or late-preterm infants with NRDS awaiting for a transfer, therefore acting on the disease as soon as possible to block its evolution or anyway to improve gas exchange and general status of the infant.

Decrease in mortality however did not result in the decrease of chronic lung disease as expected from reduction of mechanical ventilation (both as time on ventilator and as baro-volutrauma) and of oxidative stress (due to lesser time on high concentration oxygen). Neither the introduction of new and less invasive modalities and approaches to mechanical ventilation in these years did succeed in this objective. Intratracheal administration of budesonide conveyed by SF is a promising therapy to reach the target of reducing BPD [70].

Future SFs with synthetic SP analogues will certainly help the further diffusion of such therapy lowering its costs, and allowing widespread use also in bigger babies and adults that require massive doses of it.

Research on exogenous SF, it seems a rambling speech, is just at the beginning after 40 years.
References


16. [No authors listed]. Early versus delayed neonatal administration of a synthetic surfactant--the judgment of OSIRIS. The OSIRIS Collaborative Group (open study of infants at high risk of or with respiratory insufficiency--the role of surfactant. Lancet. 1992, 340(8832):1363-1369.


43. Dizdar EA, Uras N, Oguz S, Erdeve O, Sari FN et al. Total antioxidant capacity and total oxidant status after surfactant treat-


64. Herting E, Gefeller O, Land M, van Sonderen L, Harms K et al. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. Members of the Collab-


