

Guidelines for surfactant administration

Introduction

The evidence to support guidelines for the current usage of surfactant is poor. The majority of studies that can be used for guidance date from the 1980s and early 1990s when antenatal steroid usage was low, early CPAP was rarely used except in certain geographical areas, and attitudes to resuscitation of extremely premature babies were different. Most studies recruited babies by birthweight making gestational age based guidelines difficult. In compiling these guidelines there were areas in which consensus was difficult to establish. The guidelines are therefore presented as a series of brief statements. In the appendix more details are given of the areas of discussion and references provided for recommendations where appropriate. In interpretation of any guidelines it is important to remember that infants with respiratory distress in whom surfactant treatment may be indicated are a very heterogeneous group where disease severity may vary and many other confounding factors may be involved. For this reason flexibility in the guidelines is essential – what is indicated for one baby may not be for another.

Guidelines

1. Available evidence suggests that surfactant administration is associated with a highly significant reduction in mortality and air leaks in infants born at a gestational age of 25-29 weeks. Surfactant therapy should thus be considered in all infants within this gestational age range who are intubated for respiratory distress following delivery.
2. Limited evidence from randomised controlled trials on more immature infants suggests that there is short-term benefit but little impact on mortality. There are data that demonstrate significant clinical improvement in infants of 29-32 weeks, but there is very little randomised controlled trial evidence on more mature infants. It would seem appropriate to consider surfactant replacement therapy in an infant of a gestational age of 32 weeks or more who has been ventilated for respiratory distress and where surfactant deficiency is felt to be playing a significant role in the respiratory disease. It must be remembered that surfactant-deficiency may only be small part of the problem.
3. In infants at highest risk of respiratory distress syndrome – those born at a gestational age of 29 weeks or below – surfactant administration either before the first breath or soon after intubation and stabilisation appears significantly more effective than administration delayed until signs of respiratory distress develop. Available evidence cannot dictate whether true prophylaxis (before the first breath) is preferable to administration after initial resuscitation has been

- performed. There is some evidence to suggest that the latter regime conveys no disadvantage.
4. As some infants may not require respiratory support from birth it is appropriate to assess this need before surfactant treatment is initiated. The evidence to support the practice of intubation solely for the purpose of administering surfactant in an infant who would not otherwise be intubated is not conclusive and not sufficient to be able to recommend this practice.
 5. There is an increasing trend towards early initiation of continuous positive airway pressure (CPAP) without surfactant administration. There is evidence to suggest that some babies treated in this way do at least as well as those ventilated and given surfactant. There is insufficient evidence to support routine intubation and surfactant administration in those infants who are maintained on CPAP.
 6. Very early or “prophylactic” use of surfactant is recommended for all intubated infants born at a gestational age of 29 weeks or below. In those who are more mature or who are not intubated, surfactant may be administered as rescue treatment, after signs of respiratory distress develop. In this situation surfactant should be administered as soon as those signs become apparent. There is some evidence to suggest that administration of surfactant when the aAPO₂ is between 0.22 and 0.36 is associated with a reduced need for mechanical ventilation and improved outcome.
 7. Following rescue treatment the infant may either remain ventilated or be extubated onto nasal CPAP. There is no evidence to support the choice of management.
 8. The availability of postnatal surfactant administration does not reduce the need for antenatal corticosteroid administration to the mother. There are data to suggest that antenatal steroid treatment reduces the need for postnatal surfactant and has a significant additional effect on intracranial haemorrhage. Other data suggest that surfactant administration may be more effective when antenatal steroids have been given if ventilation is required.
 9. Re-treatment with surfactant should be flexible and determined by the baby’s condition. It would be appropriate to apply the same criteria for retreatment as are applied for instigation of rescue treatment. A well infant who is not ventilated and a ventilated baby requiring no more than 40% oxygen and is stable, do not need re-treatment. If a baby who is ventilated appears to deteriorate having shown improvement after a previous dose of surfactant, early re-treatment should be considered and not delayed until a set period of time has elapsed. Data sheet guidelines have not been based on evidence but the lack of evidence means that firm recommendations for the time of re-treatment cannot be made. The threshold for retreatment should be lower in infants who have RDS that is complicated by other factors such as sepsis or peri natal asphyxia.

10. A flexible approach should be adopted to the total number of doses given.
Experimental evidence suggests that no more than two doses should be given but the information which supports this may not be applicable to modern practice. Anecdotal experience suggests that a third dose may, on occasion, be beneficial but more than four doses cannot be recommended.
11. There are two animal derived surfactants currently available in the UK and no commercially available artificial surfactants. A small number of studies have compared the two available surfactants but although a difference in efficacy between the two surfactants has been demonstrated, the evidence is not sufficiently strong to make recommendations. Different surfactant preparations are available in other countries and studies using modified synthetic surfactant have been reported very recently.
12. The currently used surfactants are of bovine and porcine origin. As a life-saving drug, use should be acceptable in all circumstances. Although this is reported to be the opinion of leaders within faiths it may not be the opinion of an individual within that faith. It may also not be the opinion of individuals who are vegetarian or vegan or who have strong commitments to animal rights. The complexities of these issues are beyond the limits of these guidelines, but the issues of administration to certain groups should be considered on an individual basis.
13. Lung function may change rapidly after surfactant administration as may oxygenation. Incorrect administration may be associated with significant subsequent problems in management. Surfactant should therefore, wherever possible, be administered in units who are experienced in the administration, and in the provision of appropriate monitoring and ventilatory support. Not only should the unit have experience, but so also should the individual practitioners who administer the surfactant and care for the baby before, during and after that administration.

Discussion

1. Gestational age based recommendations are difficult to make as the randomised controlled trials were birth weight based. However, guidelines have to be pragmatic and birth weight is not a practical determinant of practice if very early administration of surfactant is to be recommended. It was thus felt that recommendations should be based on gestational age. The Cochrane database contains a number of reports on surfactant administration. In a comparison of prophylactic versus selective surfactant administration (Soll and Morley, 2001) the conclusion is that *“selective surfactant administration to infants judged to be at risk of developing respiratory syndrome (infants less than 30-32 weeks) ...has been demonstrated to improve clinical outcome.”* A review of prophylactic natural surfactant (Soll 2000) concluded that *“prophylactic intratracheal administration of natural surfactant extract to infants judged to be at risk of developing respiratory distress syndrome (intubated infants <30 weeks gestation) has been demonstrated to improve outcome.”* Other reviews simply make recommendations for administration to “high-risk” infants without defining high-risk. It would thus seem pragmatic to recommend surfactant administration to infants <30 weeks who are intubated for provision of respiratory support. Although the surfactant studies did randomise by birth weight the gestational ages were given in most and the majority of infants were within the 25-29 week bracket. Although many aspects of care have changed since these studies there is no evidence base to make radically different recommendations from these.

2. Very immature babies were excluded from the majority of surfactant studies and the evidence base to recommend administration is very limited. A meta-analysis of the published data has been reported and concludes that surfactant should be administered to the most immature babies (Soll, 1998). Another review concludes that *“There is not clear benefit of exogenous surfactant therapy in extremely premature infants (< 26 weeks gestational age, birthweight < 750 g)”* (Walti, 1998). Secondary analysis of data obtained from the Survanta trials concluded that survival was significantly improved for infants born at a gestational age between 23 and 26 weeks who received surfactant (75% vs 56%) (Hoekstra, 1994). Data from two randomised controlled trials specifically designed to examine the effect of the synthetic surfactant Exosurf showed a reduction in early mortality and mortality from respiratory distress, but no significant reduction in overall mortality and survival to discharge (Stevenson, 1992; Smyth, 1995). A large observational study from a major centre in Canada showed no secular change in overall mortality in a cohort of nearly 900 23-26 week gestational age infants following the introduction of rescue therapy with natural surfactant (Jacobs, 2000). In the EPICure study 84% of infants born at 25 weeks or below received surfactant. Surfactant administration was not associated with an improvement in outcome (Costeloe et al, 2000).

The evidence for efficacy in more mature infants is even less than for the most immature infants. One study reporting administration to 29 term infants with respiratory distress syndrome, showed an improvement in oxygenation and suggested that a randomised

controlled study should be performed (Khammash, 1993). No such study has yet been done. The two surfactants currently used in the UK – beractant and poractant – are only licensed for use in infants of 31 weeks or below and therefore any use in more mature infants would be off-licence. However, there are undoubtedly some infants who are more mature than this who are surfactant-deficient and will benefit from exogenous surfactant administration. At the same time these guidelines do not want to encourage surfactant administration in infants with mild respiratory disease and a slightly hazy X-ray. One member suggested that strict criteria should be used to define the infant who should be treated (“*a lung with generalised ground glass appearance and air bronchograms bilaterally so that it can be difficult to easily distinguish the lungs from the heart or diaphragm. This is in a baby who is working hard at their breathing, hypoxic without increased oxygen >40% and has obvious retraction of the lower ribs and sternum with inspiration*”). Others felt that they would prefer intervention before the infant had developed this degree of respiratory distress. The recommendation for further discussion was therefore that surfactant treatment should be considered in more mature infants who require ventilation for respiratory distress and, as with treatment at other gestational ages, should not be delayed once the decision to treat is made.

3. Data from randomised controlled trials are summarised in the Cochrane database and suggest significant benefit from early administration of surfactant (Soll & Morley, 2001). The latest revision concludes that ...” *Prophylactic surfactant administration to infants judged to be at risk of developing respiratory distress syndrome (intubated infants less than 30-32 weeks gestation) has been demonstrated to improve clinical outcome. Infants who receive prophylactic surfactant have a decreased incidence of pneumothorax, a decreased incidence of pulmonary interstitial emphysema and a decreased incidence of mortality. However, it remains unclear exactly which criteria should be used to judge "at risk" infants who would require prophylactic surfactant administration.*” In the trials that were included in this meta-analysis the timing of surfactant administration varied from literally before the first breath to 15 minutes or longer after birth and the comparison is therefore really between very early treatment and early rescue. Members of the group commented that the randomised controlled data are not necessarily appropriate to babies now and highlighted the fact that the definition of “prophylaxis” has never been fully established. One member recommended that prophylaxis should be given for all infants born at a gestational age at 25 to 26 weeks, but there were concerns that this could mean that a significant proportion of 26-28 week babies could be receiving rescue treatment – and this cannot be recommended. Even if the controlled trial data are not truly applicable to the current population of preterm babies, rescue therapy cannot be recommended as there is good evidence from a number of studies that outcome worsens the longer the interval before surfactant is given. The pathophysiology of respiratory distress syndrome supports the rationale of very early administration. The exact timing of “prophylactic” administration cannot be defined but probably need not be immediate and may be delayed until the infant has been resuscitated and stabilised. A three centre study compared immediate intubation and surfactant administration with intubation delayed until appropriate in the resuscitation procedure and surfactant administration at around

ten minutes (Kendig et al 1996). No difference could be demonstrated between the two groups and the authors recommended the later administration.

4. At the time that the surfactant trials were performed it is likely that a substantial proportion of the babies who were born at 29 weeks gestation or below were intubated and ventilated immediately after birth. Changes in care, including the use of antenatal steroids, have led to a larger number who do not require ventilation and intubation immediately. As this has evolved so also has the practice of intubation, followed by surfactant administration, followed by extubation. Although these guidelines recommend early administration of surfactant to “high-risk” infants it seems prudent to delay administration for long enough to assess the ventilatory needs of the individual baby and to defer administration if the baby does not appear to need positive pressure ventilation.

If intubation is not required for ventilatory support (i.e., the baby is breathing spontaneously or requiring CPAP) the evidence for intubation solely for the purpose of surfactant administration is inconclusive. This practice cannot therefore be recommended and members of the group felt very strongly that this could not be an accepted guideline. The evidence for this practice is mixed and predominantly considers the practice of elective intubation and surfactant administration followed by extubation onto CPAP when compared with selective intubation later when certain criteria for severity of illness are exceeded. A meta-analysis of four eligible trials can be found in the Cochrane Database (Stevens et al, 2004). All studies were randomized or quasi-randomised and compared early surfactant administration with a period of mechanical ventilation of no more than one hour with later selective use of surfactant with continued ventilation. The review concludes that the early treatment regime was associated with a lower incidence of mechanical ventilation and an increased usage of surfactant. No significant difference was seen in the incidence of BPD or CLD or in the duration of mechanical ventilation or supplementary oxygen. *The authors conclude that “Further research is needed to define potential limitations on the type of patients for which early surfactant with rapid extubation is appropriate (such as very premature infants <750grams) and to determine the optimal threshold of severity of respiratory distress syndrome for which to intervene with transient intubation for the purpose of surfactant administration”.* Since this review a further five-centre study has been reported (Escobedo et al, 2004). One hundred and thirty two infants who were ≥ 1250 grams and ≤ 36 weeks, who had mild to moderate RDS but no immediate need for intubation were randomized to either intubation, surfactant administration and extubation or to expectant management. Although surfactant-treated infants were less likely to require subsequent mechanical ventilation for worsening respiratory disease this was the only significant observation. The most important observation, however, was that of the 67 infants managed expectantly only 29 required mechanical ventilation. A policy of routine intubation in all infants would thus have initiated an unnecessary treatment regime in nearly 60% of the group. The infants in this study were more mature and heavier than many that are currently being cared for on neonatal intensive care units. Evidence on more immature infants is not available at present. It was felt that the practice of intubation solely to give surfactant could not be recommended at any gestation and there

were concerns that this practice could destabilize more immature infants and lead to a need for mechanical ventilation which had not existed prior to the manoeuvre.

5. The routine use of early CPAP is increasing and it is not within the remit of this section of the guidelines to comment on this practice. The practice of intubation, surfactant administration and extubation to CPAP has been reported and is used by some practitioners. The evidence base for this has been discussed in the previous section and the group felt unable to recommend the practice on the basis of currently available evidence.

6. Several studies have compared prophylactic surfactant with selective treatment and eight of these are combined in a Cochrane meta-analysis (Soll and Morley, 2001). None of these studies used the same criteria for defining the point at which surfactant should be administered in the selective group. Inspired oxygen ranged from anything more than air to an FiO_2 of 0.6; the amount of ventilatory support ranged from “requiring ventilation” to a mean airway pressure of 7 cm H_2O ; other criteria from “not having a clear X-ray to “clinical signs of RDS”. None of these criteria have been compared or tested in any study. A number of studies, both animal and human, have shown that earlier administration is associated with better outcome in many ways, and the difference in time of administration to make a difference in outcome may be an hour or less (for example Krause and Hoehn, 2000; The Osiris Collaborative Group, 1992). It is therefore obvious that surfactant should be administered as soon as a decision is made that it is needed, but the criteria to define that exact moment are unclear and for the more part not supported by a sound evidence base. Both the American Academy of Paediatrics and Canadian Paediatric Society have published guidelines for surfactant replacement therapy but both make no reference to the timing of administration (Anonymous, 1992; Anonymous, 1999). The AAP guidelines state that “An institutionally approved surfactant therapy protocol, which is a mandatory component of the quality assurance program for neonates, should exist”. The fact that clear and definitive guidelines are needed has been emphasized in a recent report of surfactant administration in 47,608 eligible infants from 347 hospitals in North America (Horbar et al, 2004). Fewer than 30% received the first dose of surfactant within 15 minutes of birth. At more than 25% of the hospitals more than 35% of the infants received their first dose of surfactant more than two hours after birth.

There is some evidence to suggest that the arterial to alveolar oxygen tension (aAPO_2) may be a useful measure to determine the point at which surfactant should be administered (Verder et al, 1999; Commentary in Hall, 1999). This study of nasal CPAP in infants <30 weeks gestation used the aAPO_2 as an index of disease severity and concluded that early treatment with surfactant when the aAPO_2 reached 0.22 to 0.36 may significantly reduce the need for mechanical ventilation. As the progression of RDS symptoms appeared to accelerate below an aAPO_2 of 0.36 the authors felt that this was an appropriate cutoff. Using an aAPO_2 of 0.36 all infants with an inspired O_2 of $\geq 50\%$ would be eligible for surfactant while there would be considerable variation below this

depending on the PaO₂. Although the evidence for the use of the aAPO₂ for this purpose is limited there is a rationale for introducing this measure into a regularly audited administration guideline rather than an arbitrary measure of FiO₂ or PaO₂ or MAP as is often used at present.

A further possibility is to target surfactant administration to those infants where there has been demonstrable surfactant deficiency. A simple bedside test for surfactant that measures the stability of bubbles in amniotic fluid or tracheal aspirate, the click-test, can be used for this purpose. In infants less than 28 weeks a positive click test lead to earlier administration of surfactant where indicated but less use of surfactant when compared to a decision to treat based upon clinical and chest radiograph criteria (Osborn et al, 2000).

7. Anecdotally it would appear that some practitioners, having decided that rescue treatment should be given, intubate, administer surfactant and extubate on to CPAP, subsequently re-intubating if the infant continues to deteriorate. There are no studies that have compared this practice with continuing mechanical ventilation after administration. The evidence with respect to prophylactic administration and extubation has been discussed above but is not comparable as the infants receiving rescue treatment will have more severe symptoms than those receiving prophylaxis. It is therefore not possible to make recommendations with respect to this issue. A recent study compared intubation, surfactant and extubation to CPAP with intubation, surfactant and mechanical ventilation (Dani et al 2004). All infants were on CPAP prior to randomization. Thirteen infants were randomized to extubation and 14 to continuing mechanical ventilation. In the CPAP group there were no babies still ventilated at seven days compared to 6 in the MV group. Mean duration of ventilation was 2 vs 5.6 days and mean duration of supplementary oxygen was 7.0 vs 11.3 days. No babies in the CPAP group needed a second dose of surfactant compared with seven in the MV group. The numbers in this study are small and infants were on CPAP prior to intubation and surfactant. The result may therefore not be applicable to rescue therapy in a baby not on CPAP prior to treatment.

8. There was unanimous agreement on this issue. There is good evidence for the benefit of antenatal corticosteroids and for the additional benefit of postnatal surfactant (Farrell et al 1989; Jobe 1993; Crowley 2000; Kent 2005). There is evidence that antenatal steroids can reduce the need for postnatal surfactant and good evidence to show that the availability of postnatal surfactant does not reduce the need for antenatal steroids.

9. Datasheets for the two surfactant preparations currently available in the United Kingdom recommend a re-treatment interval of 6-12 hours (at least 6 hours for Survanta, 6 to 12 hours after the first dose and then 12 hours later for Curosurf). These figures are not based on any evidence and cannot therefore be recommended. There will be significant differences in requirements between individual babies influenced by the severity of their respiratory disease, levels of endogenous surfactant, rate of inactivation

by inflammatory exudates and other confounding factors. It would thus be inappropriate to recommend a set interval between doses of surfactant and more appropriate to treat each infant individually and decide when to treat on the basis of the requirements of the infant at the time.

It is obviously not appropriate to retreat an infant who has been extubated but a good argument could be made for adopting the same criteria for retreatment as have been used for rescue treatment. Alternatively a higher threshold might be more appropriate for subsequent doses. This issue has been addressed in a large multicentre study from North America (Kattwinkel et al 2000). Following a first dose of surfactant 1267 neonates were randomized to either a low threshold or high threshold for retreatment. Low was defined as still intubated for RDS and requiring $\geq 30\%$ inspired oxygen to maintain a $\text{PaO}_2 \leq 80$ mm Hg while high was defined as requiring $>40\%$ inspired oxygen and a mean airway pressure >7 cm H_2O . Within each group infants were divided into uncomplicated or complicated where complicated was defined as 1) culture positive sepsis or meningitis or 2) any two of the following – amnionitis with maternal fever $>38^\circ\text{C}$; positive culture for Group B streptococcus within the last two weeks or anytime during pregnancy if accompanied by ruptured membranes for > 12 hours; clinical diagnosis of neonatal sepsis; any Apgar score ≤ 5 at 5 minutes or later; initial neonatal patient or cord gas with bicarbonate ≤ 15 mEq/L or base deficit >10 mEq/L. Infants allocated to the high-threshold had higher oxygen requirements at 72 hours after treatment but no difference in the number requiring mechanical ventilation at the same time. There were also no differences in requirement for supplementary oxygen or mechanical ventilation at 28 days, supplemental oxygen at 36 weeks postconceptional age or inspired oxygen $>60\%$ at any stage. However, a Kaplan Meier analysis suggested a trend towards a significantly higher mortality for the infants with complicated RDS when a higher threshold was used. The authors concluded that a higher threshold for retreatment was appropriate for infants with uncomplicated RDS and could result in considerable savings (an estimated saving of $>\$165,000$ in this study). In infants with complicated RDS a lower treatment threshold could be preferable.

10. Manufacturers data-sheets suggest up to three doses for Curosurf and up to four doses for Surfactant. Two studies are included in the Cochrane database meta-analysis of multiple versus single dose natural surfactant for severe neonatal respiratory distress syndrome (Soll 1999). In both studies infants were randomized to receive either a single dose of surfactant or multiple doses (up to three in one and four in the other). In one study 70% of infants received multiple doses and 65% in the other. Meta-analysis showed that the multiple dose group had a decreased requirement for ventilatory support and more sustained improvement in oxygenation and a trend towards a decrease in mortality and in pneumothoraces. It is not possible to differentiate between the efficacy of two doses or more than two doses from either the meta-analyses or the original papers. Although there is experimental evidence to suggest that there is no benefit from more than two doses of surfactant, that evidence is not strong and the group felt that a rigid policy of no more than two doses could not be proposed. Again flexibility depending upon the individual infant, the severity of the respiratory disease and the presence of

confounding factors is advocated. The large Osiris Trial randomized infants to a maximum of two doses or up to four doses and could demonstrate no benefit from the higher number. Although 2690 infants were randomized, the surfactant used – colfosceril palmitate (Exosurf) - is no longer available, first treatment could be either within the first two hours or delayed and selective and re-treatment time was no sooner than 12 hours for the second dose and 12 to 36 hours for third and fourth. It would probably be fair to suggest that these results are not reliably transferable to current practice

11. The evolution of surfactant therapy in the United Kingdom has seen the wide use of four surfactants, two synthetic and two derived from animal sources. A number of studies have compared animal-derived and synthetic surfactants and meta-analyses have been performed and shown superiority for the animal-derived products (Halliday 1996; Soll and Blanco 2001). The synthetic surfactants are no longer available. The two surfactants currently available are Beractant (Survanta) and Poractant (Curosurf). Both are used for prophylaxis and rescue with an initial and subsequent dose of Survanta of 100 mg/kg and an initial dose of Curosurf of 100-200 mg/kg and subsequent doses of 100 mg. There have been a number of relatively small studies comparing these two products. One is apparently in a thesis; one in an abstract and three have been published (Speer et al 1995; Baroutis et al 2003; Ramanathan et al, 2004). These studies have been included within a meta-analysis which suggests that Curosurf has greater efficacy than Survanta (Halliday, unpublished data). These data are not available for scrutiny and should thus be interpreted with caution. Furthermore, there should be reservations as the use of the surfactants was not comparable to the usage in current practice. Surfactant was given as a rescue treatment and benefit of Curosurf was seen with a higher starting dose of 200 mg/kg. Any benefit in this regime cannot be automatically translated to imply a benefit in a prophylaxis regime at a lower dose of 100 mg.

New synthetic surfactants are currently under development and clinical studies have been reported recently. One study of a surfactant incorporating phospholipids and recombinant surfactant protein C (Venticute) showed no significant treatment benefit of this therapy in acute RDS (Spragg et al, 2002). Minimum age for entry to this study was 19 - mean age over 50 – and results cannot be assumed to be comparable to those that might be seen in a study on premature infants. Two multicentre studies have used a different surfactant, Lucinactant, which consists of phospholipid and sinapultide, a synthetic peptide chain designed to mimic an active portion of the surfactant B molecule. In one study the synthetic surfactant is reported to show superiority to colfosceril palmitate (the synthetic surfactant, Exosurf, no longer used in the UK) and to beractant in certain measures of mortality – mortality at 14 days and all cause mortality rate at 36 weeks (Moya et al 2005). In the second study, treatment with Lucinactant is reported to be “non-inferior” to treatment with poractant (Sinha et al, 2005). Studies have been reviewed and editorials written (Kattwinkel, 2005; Moen et al, 2005). Neither product has a licence for clinical use at present, but licence application is anticipated.

12. The group were under the impression that religious leaders have expressed the opinion that as surfactant is potentially a life saving drug, it should be given when indicated. The fact that surfactants are used in countries where the animal source is normally unacceptable (poractant in Israel, for example), suggests that this is the case. The fact that leaders have expressed an opinion does not necessarily mean that the same opinion is held within a community or by an individual. It would appear that the majority of practitioner's choose not to discuss the origin of the medication with parents. In a telephone survey of 42 centres providing care only nine respondents said that they routinely discussed surfactant composition with families (Adappa et al, 2003). The majority of units had only one type of surfactant available (37 out of 41). In the same communication the authors report that two families declined to participate in a surfactant trial because of the source of the surfactant that might be used. One member of the guideline group had experience of discussion of surfactant usage with a large group of young adults from different ethnic backgrounds. Many expressed the opinion that it should be the decision of the individual and not of religious leaders. The dilemma that is raised between the medical paternalism present in non-disclosure of surfactant type and the obvious problems that would be caused, and the delay in administration, if treatment were to be discussed in full, is beyond the possible scope of these guidelines. The issues have been raised to draw attention to the problems and to encourage individual units to have their own policies, possibly drawn up after discussion with local community representatives. It has been pointed out that a potentially life-saving medication can be given against the specific wishes of a parent that it should not be. The present practice of avoiding the issue may not be the best way of dealing with it but these issues may be simplified if an effective synthetic preparation becomes commercially available.

13. Surfactant administration may result in rapid changes in lung function and oxygenation. Furthermore, infants who receive surfactant are also likely to be those who are the most sick and unstable and most likely to have multi-system disorder. In addition, incorrect surfactant administration is not without risk - unilateral pulmonary interstitial emphysema for example. The group did not feel that it was possible to make recommendations for ventilator management following surfactant administration. However, surfactant administration may only be a small part of the complex management of a sick infant and for this reason it seems appropriate to re-iterate some of the American Academy of Paediatrics Guidelines for surfactant replacement therapy for RDS (American Academy of Paediatrics. Committee on Fetus and Newborn, 1999). This document does not dwell on the technicalities of surfactant administration but stresses the importance of the environment within which the surfactant is administered. Some of the relevant points are as follows:

- i) Surfactant replacement therapy should be directed by physicians qualified and trained in its use and administration. Qualifications should include experience in management of the respiratory care of low birth weight infants, particularly those of mechanical ventilation.

- ii) Nursing and respiratory therapy personnel experienced in the management of low birth weight infants, including mechanical ventilation, should be available within the unit at the bedside when surfactant therapy is administered.
- iii) Equipment needed for managing and monitoring the condition of low birth weight infants, including that needed for mechanical ventilation, should be available on-site when surfactant therapy is administered. Radiology and laboratory support to manage a broad range of needs of these infants should be available.
- iv) More important, surfactant should be used only in institutions in which facilities and personnel are available for the management of multisystem disorders and low birth weight babies.

There is no reason to suppose that these recommendations are any less pertinent to practice in the United Kingdom.

References

Adappa R, Benson R, Oddie S, Wyllie J. Use of animal surfactant: should we seek consent? *Archives of Disease in Childhood*. 2003;88:F351

American Academy of Paediatrics. Committee on Fetus and Newborn. Surfactant replacement therapy for respiratory distress syndrome. *Pediatrics*. 1999;103:684-5

Baroutis G, Kaleyias J, Liarou T, Papathoma E, Hatzistamatiou Z, Costalos C. Comparison of three treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *European Journal of Pediatrics*. 2003;162:476-80

Canadian Paediatric Society. Fetus and Newborn Committee. Neonatal surfactant replacement therapy. *CMAJ Canadian Medical Association Journal*. 1992;146:1309-12

Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics*. 2000;106:659-71

Crowley P. Prophylactic corticosteroids for preterm birth. *Cochrane Database of Systematic Reviews*. (2):CD000065, 2000

Dani C. Bertini G. Pezzati M. Cecchi A. Caviglioli C. Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. *Pediatrics*. 113:e560-3, 2004

Easa D. Pelke S. Nakamura KT. Barrett J. Balaraman V. Loo SW. Ibarra-Pratt E. Smith MB. Exosurf treatment investigational new drug phase: effect of an individualized third dose in infants with respiratory distress syndrome. *Pediatric Pulmonology*. 1992;14:16-22

Escobedo MB. Gunkel JH. Kennedy KA. Shattuck KE. Sanchez PJ. Seidner S. Hensley G. Cochran CK. Moya F. Morris B. Denson S. Stribley R. Naqvi M. Lasky RE. Texas Neonatal Research Group. Early surfactant for neonates with mild to moderate respiratory distress syndrome: a multicenter, randomized trial. *Journal of Pediatrics*. 2004;144:804-8,

Farrell EE. Silver RK. Kimberlin LV. Wolf ES. Dusik JM. Impact of antenatal dexamethasone administration on respiratory distress syndrome in surfactant-treated infants. *American Journal of Obstetrics & Gynecology*. 1989;161:628-33

Figueras-Aloy J. Quero J. Carbonell-Estrany X. Ginovart G. Perez-Rodriguez J. Raspall F. Rodriguez Miguelez JM. Salvia MD. Early administration of the second dose of surfactant (beractant) in the treatment of severe hyaline membrane disease. *Acta Paediatrica*. 2001;90:296-301

Hall RT. Indications for surfactant therapy-the aAPO2 coming of age. *Pediatrics*. 1999;103:E25

Halliday HL. Natural vs synthetic surfactants in neonatal respiratory distress syndrome. *Drugs*. 1996;51:226-37

Hoekstra RE. Ferrara TB. Payne NR. Effects of surfactant therapy on outcome of extremely premature infants. *European Journal of Pediatrics*. 1994;153:S12-6

Horbar JD. Carpenter JH. Buzas J. Soll RF. Suresh G. Bracken MB. Leviton LC. Plsek PE. Sinclair JC. Vermont Oxford Network. Timing of initial surfactant treatment for infants 23 to 29 weeks' gestation: is routine practice evidence based?. *Pediatrics*. 2004;113:1593-602

Jacobs SE. O'Brien K. Inwood S. Kelly EN. Whyte HE. Outcome of infants 23-26 weeks' gestation pre and post surfactant. *Acta Paediatrica*. 2000;89:959-65

Jobe AH. Mitchell BR. Gunkel JH. Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. *American Journal of Obstetrics & Gynecology*. 1993;168:508-13

Kattwinkel J. Bloom BT. Delmore P. Glick C. Brown D. Lopez S. Willett L. Egan EA. Conaway M. Patrie J. High-versus low-threshold surfactant retreatment for neonatal respiratory distress syndrome. *Pediatrics*. 2000;106:282-8

Kattwinkel J. Synthetic surfactants: the search goes on. *Pediatrics*. 2005;115:1075-6

Kendig JW. Ryan RM. Sinkin RA. Maniscalco WM. Notter RH. Guillet R. Cox C. Dweck HS. Horgan MJ. Reubens LJ. Risemberg H. Phelps DL. Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. *Pediatrics*. 1998;101:1006-12

Kent A. Lomas F. Hurrion E. Dahlstrom JE. Antenatal steroids may reduce adverse neurological outcome following chorioamnionitis: neurodevelopmental outcome and chorioamnionitis in premature infants. *Journal of Paediatrics & Child Health*. 2005;41:186-90

Khammash H. Perlman M. Wojtulewicz J. Dunn M. Surfactant therapy in full-term neonates with severe respiratory failure. *Pediatrics*. 1993;92:135-9

Krause MF. Hoehn T. Timing of surfactant administration determines its physiologic response in a rabbit model of airway lavage. *Biology of the Neonate*. 2000;77:196-202

Moen MD. Perry CM. Wellington K. Lucinactant: in neonatal respiratory distress syndrome. *Treatments in Respiratory Medicine*. 2005;4:139-45

Moya FR. Gadzinowski J. Bancalari E. Salinas V. Kopelman B. Bancalari A. Kornacka MK. Merritt TA. Segal R. Schaber CJ. Tsai H. Massaro J. d'Agostino R. International Surfaxin Collaborative Study Group. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics*. 2005;115:1018-29

Osborn DA. Jeffery HE. Bredemeyer SL. Polverino JM. Reid S. Targeted early rescue surfactant in ventilated preterm infants using the click test. *Pediatrics*. 2000;106:E30

Ramanathan R. Rasmussen MR. Gerstmann DR. Finer N. Sekar K. North American Study Group. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. *American Journal of Perinatology*. 2004;21:109-19,

Smyth J. Allen A. MacMurray B. Peliowski A. Sankaran K. Volberg F. Shukla A. Long W. Double-blind, randomized, placebo-controlled Canadian multicenter trial of two doses of synthetic surfactant or air placebo in 224 infants weighing 500 to 749 grams with respiratory distress syndrome. Canadian Exosurf Neonatal Study Group. *Journal of Pediatrics*. 1995;126:S81-9

Sinha SK. Lacaze-Masmonteil T. Valls i Soler A. Wiswell TE. Gadzinowski J. Hajdu J. Bernstein G. Sanchez-Luna M. Segal R. Schaber CJ. Massaro J. d'Agostino R. Surfaxin Therapy Against Respiratory Distress Syndrome Collaborative Group. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics*. 2005;115: 1030-8

Soll RF. Surfactant treatment of the very preterm infant. *Biology of the Neonate*. 1998;74 Suppl 1:35-42

Soll RF. Multiple versus single dose natural surfactant extract for severe neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews*. 2000;CD000141

Soll RF. Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews*. 2001;CD000144

Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*. 2000;CD000511

Soll RF. Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*. 2001;CD000510

Speer CP. Gefeller O. Groneck P. Laufkotter E. Roll C. Hanssler L. Harms K. Herting E. Boenisch H. Windeler J. et al. Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *Archives of Disease in Childhood* 1995;72:F8-13

Spragg RG. Lewis JF. Wurst W. Hafner D. Baughman RP. Wewers MD. Marsh JJ. Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. *American Journal of Respiratory & Critical Care Medicine*. 2003;167:1562-6

Stevens TP. Blennow M. Soll RF. Early surfactant administration with brief ventilation vs selective surfactant and continued mechanical ventilation for preterm infants with or at risk for RDS. *Cochrane Database of Systematic Reviews*. 2002;CD003063,

Stevenson D. Walther F. Long W. Sell M. Pauly T. Gong A. Easa D. Pramanik A. LeBlanc M. Anday E. et al. Controlled trial of a single dose of synthetic surfactant at birth in premature infants weighing 500 to 699 grams. The American Exosurf Neonatal Study Group. *Journal of Pediatrics*. 1992;120:S3-12

The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant--the judgment of OSIRIS (open study of infants at high risk of or with respiratory insufficiency--the role of surfactant). *Lancet*. 1992;340:1363-9

Verder H. Albertsen P. Ebbesen F. Greisen G. Robertson B. Bertelsen A. Agertoft L. Djernes B. Nathan E. Reinholdt J. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics*. 1999;103(2):E24

Walti H. Monset-Couchard M. A risk-benefit assessment of natural and synthetic exogenous surfactants in the management of neonatal respiratory distress syndrome. *Drug Safety*. 1998;18:321-3