

Recommendations for neonatal surfactant therapy



Canadian Paediatric Society
Français en page 119

Exogenous surfactant therapy has become well established in newborn infants with respiratory distress. Many aspects of its use have been well evaluated in high-quality trials and systematic reviews. This statement summarizes the evidence and gives recommendations for the use of surfactant therapy in a variety of clinical situations.

BACKGROUND

In 1959, Avery and Mead (1) reported on the deficiency of surface-active material in the lungs of preterm babies with respiratory distress syndrome (RDS). This led to clinical trials of artificial surface-active materials in babies with RDS (2,3). Surfactants have since been studied in several large, well-designed randomized controlled trials (RCTs), which make possible this comprehensive analysis of indications, risks and benefits.

METHODS OF STATEMENT DEVELOPMENT

Systematic reviews were sought from the Cochrane Database of Systematic Reviews (Cochrane Collaboration) (4) and the Database of Abstracts of Reviews of Effectiveness (DARE) (University of York, York, United Kingdom). For aspects of surfactant replacement that were not investigated in reviews, MEDLINE was searched for the years 1986 to 2003, and all available RCTs addressing these aspects were reviewed. The specific issues included the role of surfactants in pulmonary hemorrhage and neonatal pneumonias; the use of antenatal steroids in combination with surfactant therapy; and the frequency of, and indications for, retreatment. The search was limited to articles addressing human newborns in English, French, German or Spanish. The following questions about the optimal use of surfactant replacement therapy were addressed using information from the literature review described above.

WHAT ARE THE INDICATIONS FOR AND BENEFITS OF SURFACTANT REPLACEMENT THERAPY?

RDS is usually defined by the presence of acute respiratory distress with disturbed gas exchange in a preterm infant with a typical clinical course or x-ray (ground glass appearance, air bronchograms and reduced lung volume). The lungs of preterm babies with RDS are both anatomically and biochemically immature; they neither synthesize nor secrete

surfactant well. Surfactant normally lines the alveolar surfaces in the lung, thereby reducing surface tension and preventing atelectasis. Surfactant replacement therapy, either as a rescue treatment or a prophylactic natural surfactant therapy, reduces mortality (evidence level 1a [Table 1]) and several aspects of morbidity in babies with RDS (5-13). These morbidities include deficits in oxygenation, the incidence of pulmonary air leaks (pneumothorax and pulmonary interstitial emphysema) and the duration of ventilatory support (evidence level 1a). Surfactant replacement increases the likelihood of surviving without bronchopulmonary dysplasia (BPD, also known as chronic lung disease of the preterm) largely by improving survival rather than the incidence of BPD. Babies treated with surfactants have shorter hospital stays and lower costs of intensive care treatment (14-19) compared with randomized control infants receiving no surfactants. The increase in survival is achieved with no increase in adverse neurodevelopmental outcome (evidence level 1a).

TABLE 1
Levels of evidence used in this statement

Level of evidence	
1a	Systematic review (with homogeneity) of randomized controlled trials
1b	Individual randomized controlled trial (with narrow CI)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (or low-quality randomized controlled trial, eg, <80% follow-up)
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'
Grade of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies
C	Level 4 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Recommendation

- Intubated infants with RDS should receive exogenous surfactant therapy (grade A).

Secondary surfactant deficiency or dysfunction occurs in other newborn respiratory disorders, including meconium aspiration syndrome, pneumonia and pulmonary hemorrhage. A variety of substances, including albumin, meconium and blood inhibit surfactant function (20-22). Two RCTs (23,24) in babies with severe meconium aspiration syndrome have shown the benefits of surfactant replacement therapy. One studied infants requiring 100% oxygen with an oxygenation index greater than 15 (24), and the other studied infants requiring more than 50% oxygen with an arterial/alveolar O₂ tension ratio of less than 0.22 (23). A systematic review reported no differences in mortality or pneumothorax but it showed a decrease in the requirement for extracorporeal oxygenation (25) (evidence level 1a).

Recommendation

- Intubated infants with meconium aspiration syndrome requiring more than 50% oxygen should receive exogenous surfactant therapy (grade A).

Surfactant lavage for meconium aspiration syndrome could be effective but requires further study because there has been only one small controlled trial (26) showing possible short-term physiological benefits and no clinically significant benefits when compared with a group with restricted rescue surfactant therapy.

The use of surfactant replacement therapy in neonatal pneumonia has not been adequately studied. A subgroup analysis of near-term babies with respiratory failure from the prospective RCT of Lotze et al (24), showed that those who had sepsis and were treated with surfactants had a 40% decrease in the need for extracorporeal membrane oxygenation. Other case series of neonatal bacterial pneumonia appear to show surfactant therapy to be beneficial (27-29) (evidence level 4).

Recommendation

- Sick newborn infants with pneumonia and an oxygenation index greater than 15 should receive exogenous surfactant therapy (grade C).

In controlled trials, exogenous surfactant therapy increases the incidence of pulmonary hemorrhage (30). However, because haemoglobin and other blood components such as fibrinogen have been shown to have serious adverse effects on surfactant function (31), surfactant replacement therapy has also been used to treat pulmonary hemorrhage. There are no RCTs examining the use of surfactant replacement therapy in this condition. Pulmonary hemorrhage is often very acute and unpredictable, and leads to rapid deterioration, which would make a formal RCT difficult. However, the incidence of pulmonary hemorrhage in the most immature infants is as high as 28%, suggesting that there may be opportunity for a focussed trial in the future (32). One retrospective cohort study showed a substantial acute improvement

in oxygenation in babies with pulmonary hemorrhage who had significant clinical compromise when they were given surfactant replacement therapy (33) (evidence level 4).

Recommendation

- Intubated newborn infants with pulmonary hemorrhage which leads to clinical deterioration should receive exogenous surfactant therapy as one aspect of clinical care (grade C).

Finally, for lung hypoplasia and congenital diaphragmatic hernia, only small case series have been reported (34,35) and no conclusions can be made.

WHAT ARE THE RISKS OF EXOGENOUS SURFACTANT THERAPY?

The short-term risks of surfactant replacement therapy include bradycardia and hypoxemia during instillation, as well as blockage of the endotracheal tube (36). There may also be an increase in pulmonary hemorrhage following surfactant treatment; however, mortality ascribed to pulmonary hemorrhage is not increased (37) and overall mortality is lower after surfactant therapy. The RR for pulmonary hemorrhage following surfactant treatment has been reported at approximately 1.47 (95% CI 1.05 to 2.07) in trials (30) but, unfortunately, many of the RCTs on surfactant replacement have not reported this outcome, nor have the data from autopsy studies clearly defined the magnitude of this risk (38-40) (evidence level 1a). No other adverse clinical outcome has been shown to be increased by surfactant therapy.

There is often a very rapid improvement in gas exchange in surfactant-treated infants who are surfactant deficient. This is accompanied by dramatic improvements in static pulmonary compliance (41,42). In contrast, when dynamic compliance is measured, there is little acute change detected (43). This discrepancy is explained by the large increase in functional residual capacity due to the recruitment of lung volume (evidence level 1b). Therefore, the pressure volume loops of the lung are normalized, but unless administered pressures are reduced, overdistension can occur. Hyperventilation with very low PCO₂ can also sometimes accidentally occur. Thus, weaning of administered airway pressures and ventilator settings should be expected within a few minutes of the administration of natural surfactants, and the caregivers must be aware of the nature and speed of these changes.

Natural surfactants contain proteins (surfactant protein-A, surfactant protein-B) from bovine or porcine sources and questions have been raised about the immunological effects. To date, there is no evidence that there are immunological changes of clinical concern. Babies with RDS have detectable circulating immune complexes directed toward surfactant proteins, but these do not appear to be more frequent in babies that are treated with surfactants (44-48). One study (44) showed a lower incidence of anti-surfactant protein-A and antisurfactant protein-B in babies treated with surfactant compared with controls. The small number of patients that have been followed long term do

not show detectable levels of antibodies to exogenous surfactant proteins (49). There may be family preferences for particular sources of surfactants, given the animal nature of the sources. This is rarely a problem in day-to-day practice but should be approached sensitively.

Approved surfactants are produced in accordance with regulated standards of microbiological safety. However, given the uncertainty about the methods of transmission of emerging pathogens such as prions, no comment can be made at the present time about the potential transmission of such agents.

WHICH IS BETTER:

NATURAL OR SYNTHETIC SURFACTANTS?

A total of 11 randomized studies comparing natural to synthetic surfactants for babies with RDS have been subject to systematic review (10). The review showed that overall mortality is decreased by the use of natural surfactants compared with synthetic surfactants (RR of death = 0.86, 95% CI 0.75 to 0.99; absolute risk difference (ARD) = 0.025, 95% CI -0.047 to -0.003; number needed to treat (NNT) with natural surfactants rather than synthetic surfactants to prevent one death = 40, 95% CI 21 to 333). Most of the studies showed that babies treated with natural surfactants have lower needs for oxygen and ventilatory support for at least three days following dosing compared with babies treated with synthetic surfactants. Pulmonary air leak syndrome is less common in babies treated with natural surfactants (RR of pneumothorax = 0.63, 95% CI 0.52 to 0.76; ARD=0.044, 95% CI -0.061 to -0.027; NNT=23, 95% CI 16 to 37; evidence level 1a). The incidence of BPD is not different in babies given natural or synthetic surfactants, but because mortality is reduced in babies given natural surfactants, the combined outcome of death or BPD is reduced (RR=0.95, 95% CI 0.90 to 1.01). There is a paucity of information about long-term outcomes comparing babies treated with natural or synthetic surfactants.

Therefore, natural surfactants improve survival without BPD and with a lower incidence of airleak, and they are to be preferred over synthetic surfactants (evidence level 1a). However, it must be noted that all studies comparing natural with synthetic surfactants have been done using synthetic preparations that did not contain surfactant protein analogues. New synthetic surfactants have been developed which may have enhanced efficacy and they are presently being investigated in clinical trials.

Recommendation

- Natural surfactants should be used in preference to any of the synthetic surfactants available at the time of publication of this statement (grade A).

WHICH IS BETTER: SURFACTANTS GIVEN AS PROPHYLAXIS OR RESCUE THERAPY FOR PRETERM BABIES WITH RDS?

A number of studies have evaluated whether surfactant should be given to all babies at significant risk for developing RDS or only after the development of significant disease. Soll

and Morley (50) reviewed seven RCTs of prophylactic versus rescue therapy. These were all trials that used natural surfactants. Six of the RCTs enrolled babies less than 30 weeks of gestation and one enrolled babies of 29 to 32 weeks of gestation. Mortality, both before 28 days and before hospital discharge, was reduced by prophylactic surfactant treatment (evidence level 1a) (RR of neonatal mortality = 0.61, 95% CI 0.48 to 0.77; ARD=-0.046, 95% CI -0.067 to -0.024; NNT=22, 95% CI 15 to 42). The incidence of RDS, pneumothorax (RR=0.62, 95% CI 0.42 to 0.89; ARD=-0.021, 95% CI -0.037 to -0.005; NNT=50, 95% CI 27 to 200) and pulmonary interstitial emphysema (RR=0.54, 95% CI 0.36 to 0.82; ARD=-0.026, 95% CI -0.043 to -0.009; NNT=38, 95% CI 23 to 111) were all decreased in babies treated prophylactically. There was no difference in the incidence of BPD, although the combined outcome of BPD or death did show a decrease in babies treated prophylactically. No differences were noted in the incidences of patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity or severe intraventricular hemorrhage. The meta-analysis (50) indicated that there would be two fewer pneumothoraces and five fewer deaths for every 100 babies treated prophylactically with surfactant. If a prophylactic treatment approach is used for all infants of less than 32 weeks gestation, approximately twice as many babies at risk for RDS will receive surfactant therapy than if a rescue approach is used.

In a multicentre RCT with 651 infants, Kendig et al (51) showed that there was no clinically significant difference in outcome between immediate administration of prophylactic surfactant and administration at 10 min after birth after a brief period of stabilization (evidence level 1b). However, giving the surfactant as soon as possible once stabilization has occurred seems to be important. The open study of infants at high risk of or with respiratory insufficiency – the role of surfactant (OSIRIS) (52) demonstrated that the combined incidence of death or BPD was reduced by about 11% when surfactant was given at a mean postnatal age of 2 h rather than 3 h (RR=0.89, 95% CI 0.79 to 1.00, evidence level 1b), showing that even fairly short delays in therapy worsen outcomes (evidence level 1b).

It should be noted that the RR of death appears to be very similar whatever the underlying risk. However, the absolute risk of death, and, therefore, the NNT, will differ according to the absolute risk among untreated patients. For example, in the Cochrane meta-analysis (50), the RR is identical for the whole group (0.61) and for infants of less than 30 weeks of gestation (0.62), despite different ARDs (0.11 versus 0.16). The decision to intervene with prophylactic surfactant should depend on the availability of competent personnel and centre-specific mortality rates. It should be noted that very early rescue (eg, 30-min- to 45-min-old) has not been adequately studied, specifically in comparison with a truly prophylactic approach.

The usage of antenatal steroids was not reported for two of the studies reviewed by Soll and Morley (50). In the remainder of the studies, antenatal steroid use ranged from 14% to 50%, which is considerably less than current usage.

The RR of death for prophylactic compared with rescue surfactant therapy does not appear to be related to the frequency of steroid treatment; however, the ARD that can be expected will differ based on the underlying risk, which is affected by antenatal steroids. With the current mortality rates at tertiary centres, a reasonable option would be to give surfactant prophylactically to all infants less than 26 weeks gestation, and to those of 26 to 27 weeks gestation who have not received the benefit of antenatal steroids.

No prospective RCTs have evaluated prophylactic synthetic surfactant.

Recommendation

- Infants who are at a significant risk of RDS should receive prophylactic natural surfactant therapy as soon as they are stable within a few minutes after intubation (grade A).

For patients not considered candidates for prophylaxis, other supplemental rapid tests of surfactant deficiency may be beneficial. There are no randomized comparisons of the use of such tests in the determination of who would benefit from surfactant treatment.

HOW SHOULD THE SURFACTANT REPLACEMENT THERAPY BE GIVEN?

For all of the surfactant replacement therapy trials, surfactant was instilled in liquid form via the endotracheal tube. Some trials instilled all of the surfactant at once, while others instilled it in smaller aliquots. Only one very small trial (53) compared a slow infusion with bolus administration of surfactant. It concluded that slow infusion was at least as effective as bolus therapy.

There is no evidence to support the practice of placing the infant in multiple different positions during the administration of surfactant.

WHAT DOSAGE SHOULD BE USED?

Dosages have varied from 25 mg to 200 mg phospholipids/kg body weight as single doses in the different clinical trials. Studies of different dosing regimens are limited. Surfactant-TA (a natural bovine surfactant) was more effective at a dose of 120 mg/kg than 60 mg/kg (54). Curosurf (Chiesi Pharmaceuticals, Italy) (a natural porcine surfactant) was more effective acutely at 200 mg/kg than 100 mg/kg (55). It may well be that lower doses would be appropriate for prophylaxis while higher doses might be required for treatment of established RDS when surfactant inhibitors are present in the airspaces. This has not been empirically evaluated, but would be consistent with data showing a lower total dose requirement in infants treated prophylactically compared with rescue therapy. Thus, it appears that improvements in outcomes are seen up to a dose of about 120 mg phospholipids/kg body weight for the first dose, larger initial doses do not lead to further improvements in outcomes (evidence level 1b, from summation of results of various trials, without formal systematic review).

SHOULD MULTIPLE OR SINGLE DOSES OF SURFACTANT BE USED?

Two trials of multiple versus single doses of surfactant replacement therapy (which included 394 babies in total) have been reviewed (56). These studies compared infants treated with a single dose with either retreatment with up to three doses within the first 72 h for infants who had a deterioration (shown by a 0.1 increase in the fraction of inspired oxygen [FiO_2] after an initial response) (57) or retreatment with up to three doses at 12 h and 24 h after the initial dose for infants who remained intubated and required oxygen (58). It should be noted that the babies studied were a heterogeneous group with gestational ages that ranged from 30 to 36 weeks in one study and a birth-weight range of 700 g to 2000 g in the other. Meta-analysis of the trials showed a reduction in the risk of pneumothorax (RR=0.51, 95% CI 0.30 to 0.88; ARD=-0.09, 95% CI -0.15 to -0.02) and a trend toward a reduction in mortality (RR=0.63, 95% CI 0.39 to 1.02; ARD=-0.07, 95% CI -0.14 to 0.0). No complications associated with multiple dose treatment were identified (evidence level 1a).

Recommendation

- Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements within the first 72 h of life should have repeated doses of surfactant. Administering more than three doses has not been shown to have a benefit (grade A).

One RCT (59) showed that for synthetic surfactants, babies who received three prophylactic doses rather than one had decreased oxygen and ventilatory needs in the first week of life and lower mortality at 28 days and one year of life (evidence level 1b).

WHAT ARE THE CRITERIA FOR, AND TIMING OF, RETREATMENT?

There are extremely limited data comparing the different criteria for retreatment (they were decided arbitrarily in the two trials referenced above) (57). Kattwinkel et al (60) compared the relative efficacy of administering second and subsequent doses of a natural surfactant at low (FiO_2 greater than 0.30, still requiring intubation) and high (FiO_2 greater than 0.40, mean airway pressure greater than 7 cm H_2O) thresholds after a minimum of 6 h. They noted no benefits from retreating at the lower threshold, except in those babies with complicated RDS (evidence of perinatal compromise or sepsis) who had a lower mortality with low threshold retreatment (evidence level 1b).

Retreatment strategies may be dependent on which preparation is used, as some are more prone to protein inactivation. The timing of retreatment has been fairly arbitrarily determined in most of the surfactant trials, but comparisons of the timing of retreatment have been limited and there have been no comparisons of the timing of retreatment between surfactant preparations.

Figueras-Aloy et al (61) randomly compared retreatment at 2 h and 6 h after the initial dose. There appeared to be some short-term advantages to earlier redosing in the smallest infants, but the study was small and no clinically important benefits were shown (evidence level 2).

Recommendation

- Retreatment should be considered when there is a persistent or recurrent oxygen requirement of 30% or more and it may be given as early as 2 h after the initial dose or, more commonly, 4 h to 6 h after the initial dose (grade A).

HOW SHOULD VENTILATORY MANAGEMENT AFTER SURFACTANT THERAPY BE APPROACHED?

Because of the rapid changes in lung mechanics and the ventilation/perfusion matching that occurs after rescue surfactant therapy, and the prevention of serious lung disease by the prophylactic use of natural surfactants, many infants can be very rapidly weaned and extubated to nasal continuous positive airway pressure (CPAP) within 1 h of intubation and surfactant administration. To do this, the premedication used for intubation should only cause a brief duration of respiratory depression and staff must be trained and skilled in rapid ventilator weaning. Such weaning is often performed with few or no blood gases, relying instead on the infant's clinical condition and spontaneous respiratory effort and with consideration of the oxygen requirements as determined from pulse oximetry and sometimes with the use of transcutaneous CO₂ measurements.

There is currently no proof that a rapid wean and extubation approach improves long-term outcomes compared with the more traditional weaning approach. In two small randomized trials (62,63), such an approach led to a decrease in the need for more than 1 h of mechanical ventilation (evidence level 2b). Definitive recommendations will require further evidence.

Recommendation

- Options for ventilatory management that are to be considered after prophylactic surfactant therapy include very rapid weaning and extubation to CPAP within 1 h (grade B).

IF WE CAN GIVE SURFACTANT THERAPY, DO WE STILL NEED TO USE ANTENATAL STEROIDS?

According to current guidelines (64), expectant mothers with threatened preterm labour should be given a single course of steroids. Large cohort studies indicate that the combination of surfactant and steroids is more effective than exogenous surfactant alone (65) (evidence level 2b). A secondary analysis of data from surfactant trials also indicates a reduction in disease severity in babies who received antenatal steroids (66) (evidence level 4). Two other RCTs

(67,68) have confirmed that antenatal steroids continue to reduce the risk of poor outcome, even in centres where surfactant is available; one (69) showed a reduction in RDS as well as an increase in survival without ventilatory support and both showed significant reductions in severe intraventricular hemorrhage.

Recommendation

- According to established guidelines (64), mothers at risk of delivering babies with less than 34 weeks gestation should be given antenatal steroids regardless of the availability of postnatal surfactant therapy (grade A).

SHOULD SURFACTANT THERAPY BE GIVEN BEFORE THE TRANSPORT OF A BABY WITH RDS?

Administration of surfactants to preterm babies before transport has been studied retrospectively and was found to be safe (69,70). There were no major improvements in morbidity or mortality, although in one of the studies (70) there were lower oxygen requirements during transport and fewer days of ventilation compared with a concurrent retrospective control group (evidence level 3b). Prospective studies would be required to clearly determine whether outcomes are improved if surfactant is given before transport. The significantly reduced risk for pneumothorax after surfactant therapy is a potential benefit, given the difficulties of managing this complication during transport.

Recommendation

- Intubated infants with RDS should receive exogenous surfactant therapy before transport (grade C).

If surfactant therapy is to be given before transport, which may be beneficial given the distances to referral hospitals in some parts of Canada, the health care workers must be skilled in neonatal intubation, understand the changes in lung compliance and ventilation that can occur following surfactant use, and know the potential short-term side effects of surfactant replacement therapy. Constant on-site availability of personnel trained and licensed to deal with the possible complications is essential (evidence level 5).

Recommendation

- Centres administering surfactant therapy to newborn infants must ensure the continuous on-site availability of personnel that are competent and licensed to deal with the acute complications of assisted ventilation and surfactant therapy (grade D).

Given that not many at-risk babies are born in peripheral hospitals, regional networks should develop surfactant exchange programs so that this medication can be used in a cost-effective manner. For example, surfactants nearing expiration could be exchanged with the local tertiary centre for a new vial.

Although surfactant therapy can be very beneficial in the stabilization of these babies, it does not alleviate the multisystem dysfunction that these babies may have.

Surfactant replacement therapy should not change the frequency of referral of high-risk, low birth weight babies to nurseries that have the full range of expertise and resources to care for them.

HOW SHOULD SURFACTANT REPLACEMENT THERAPY BE USED OUTSIDE A TERTIARY CENTRE?

Very preterm infants (less than 32 weeks gestation) delivered outside of a tertiary centre have increased mortality and long-term morbidity (71) (evidence level 2b). Every effort should be made to give antenatal steroids (according to current recommendations) and transfer mothers with threatened delivery before 32 weeks gestation to a centre with a level 3 neonatal intensive care unit before delivery, regardless of the availability of surfactants. If this is not possible because of pending delivery, the decision to intubate prophylactically for surfactant administration should follow the principles outlined above. Mothers delivering outside a tertiary centre will usually have insufficient time for antenatal steroids to be effective and, therefore, the infants have a greatly increased odds (OR=4.6, 95% CI 3.6 to 6.3) of developing RDS. On the other hand, the availability of experienced, competent and appropriately licensed personnel needs to be considered, as does the delay in the attendance of the tertiary transport team.

Randomized trials of surfactant prophylaxis were generally performed in tertiary centres where the risk-benefit ratio may differ from other centres. Therefore, we make a pragmatic recommendation that after unavoidable deliveries at a level 2 centre at less than 29 weeks gestation, infants should be considered for prophylactic natural surfactant therapy as soon as they are stable within a few minutes after intubation.

Considering that the immaturity of their other organ functions requires the close monitoring and specialized care available in tertiary centres to ensure optimal outcomes, infants who receive surfactant therapy should be transferred to a tertiary centre afterward, even though many such infants will have little residual lung disease.

Recommendation

- Mothers with threatened delivery before 32 weeks gestation should be transferred to a tertiary centre if at all possible (grade B).
- Infants who deliver at less than 29 weeks gestation outside of a tertiary centre should be considered for immediate intubation followed by surfactant administration after stabilization, if competent personnel are available (grade A).

SUMMARY

Exogenous surfactant therapy is safe and has major benefits in the treatment of several respiratory diseases in the newborn. It has been well studied in RCTs of excellent quality, which have clearly documented that its administration

should be standard in the treatment of RDS and as prophylaxis in identified groups of preterm babies. Evidence continues to be accumulated for its use in other newborn respiratory diseases. The Canadian Paediatric Society makes the following recommendations.

RECOMMENDATIONS

- Mothers at risk of delivering babies with less than 34 weeks gestation should be given antenatal steroids according to established guidelines (64) regardless of the availability of postnatal surfactant therapy (grade A).
- Intubated infants with RDS should receive exogenous surfactant therapy (grade A).
- Intubated infants with meconium aspiration syndrome requiring more than 50% oxygen should receive exogenous surfactant therapy (grade A).
- Sick newborn infants with pneumonia and an oxygenation index greater than 15 should receive exogenous surfactant therapy (grade C).
- Intubated newborn infants with pulmonary hemorrhage which leads to clinical deterioration should receive exogenous surfactant therapy as one aspect of clinical care (grade C).
- Natural surfactants should be used in preference to any of the artificial surfactants available at the time of publication of this statement (grade A).
- Infants who are at a significant risk for RDS should receive prophylactic natural surfactant therapy as soon as they are stable within a few minutes after intubation (grade A).
- Infants with RDS who have persistent or recurrent oxygen and ventilatory requirements within the first 72 h of life should have repeated doses of surfactant. Administering more than three doses has not been shown to have a benefit (grade A).
- Retreatment should be considered when there is a persistent or recurrent oxygen requirement of 30% or more, and it may be given as early as 2 h after the initial dose or, more commonly, 4 h to 6 h after the initial dose (grade A).
- Options for ventilatory management that are to be considered after prophylactic surfactant therapy include very rapid weaning and extubation to CPAP within 1 h (grade B).
- Intubated infants with RDS should receive exogenous surfactant therapy before transport (grade C).
- Centres administering surfactant to newborn infants must ensure the continuous on-site availability of personnel competent and licensed to deal with the acute complications of assisted ventilation and surfactant therapy (grade D).

- Mothers with threatened delivery before 32 weeks gestation should be transferred to a tertiary centre if at all possible (grade B).
- Infants who deliver at less than 29 weeks gestation outside of a tertiary centre should be considered for immediate intubation followed by surfactant administration after stabilization, if competent personnel are available (grade A).
- Further research into retreatment criteria and the optimal timing of prophylactic therapy is required.

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Principal authors: Drs Deborah J Davis, *Bispebjerg Hospital, Kobanham NV Denmark*; Keith J Barrington, *Royal Victoria Hospital, Montreal, Québec*

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.