

Case Based Teaching – Respiratory Distress  
St. Joseph's CTU

Objectives:

Medical Expert:

1. Review the different causes of respiratory distress in a newborn
2. Understand the differences between pulmonary and cardiac causes of respiratory distress
3. Review the initial investigations to work come to a diagnosis
4. Understand the benefits and risks of surfactant in RDS
5. Understand the benefits and risks of pre-natal steroids for respiratory distress syndrome

Communicator:

1. Learn how to explain to parents the potential causes of respiratory distress in the newborn period
2. Learn the information needed to counsel around surfactant and injected steroids for newborns with RDS

Resources:

1. Flidel-Rimon, O et al. Respiratory Distress in the Term and Near-term Infant. NeoReviews. 2005;6;e289
2. Warren, JB et al. Respiratory Distress Syndrome. NeoReviews. 2009;10;e351.
3. SOGC Guidelines. Antenatal Corticosteroids for Fetal Maturation. No. 122. January 2003.
4. CPS Position Statement. Recommendations for neonatal surfactant therapy. FN 2005-01.

Case Review:

You are on call at St. Joseph's Hospital for Level 2 Nursery and are called to a delivery at 2:00am. There is a G1 mom about to deliver at 35 weeks and L and D wants pediatrics there for newborn care following delivery.

You arrive to the delivery room moments before the baby is born, get a chance to introduce yourself to the parents, and set up your equipment for potential resuscitation including oxygen, bag and mask, suction, towels to dry, intubation equipment.

A baby comes out and cries spontaneously. You let out a sigh of relief, and the baby is brought over to the warmer to be dried and examined before going back to parents.

You receive baby, and start to warm, dry and stimulate. She is crying. You check a heart rate which is 120 – 'nice' you think.

As you get her dried off, and let dad cut the umbilical cord she starts to grunt intermittently and you notice some subtle findings of increased work of breathing.

Discussion:

What are the signs of work of breathing in a newborn?

What would your differential be for increased work of breathing in a newborn? Does it change if the baby was 30 weeks GA? What about if baby was 48 hours old?

What else do you want to know on history? Physical exam?

Case:

The baby is now indrawing both subcostally and intercostally quite significantly. She has nasal flaring and is continuously grunting. Her respiratory rate is 85 breaths per minute. You are able to get an O<sub>2</sub> sat probe on and fortunately it has a good wavelength. Her saturations are 84% on blow by O<sub>2</sub>. She has a systolic murmur gr 2/6 loudest at the LUSB.

You quickly get some additional antenatal history from mom. This is her first child and was a planned pregnancy. Mom had good antenatal follow up and had a normal IPS screen, normal 20 week U/S and protective serology including rubella immune, HIV negative, VDRL negative, hepatitis negative. GBS status is unknown as mom had not yet had swabs done.

Mom had GDM, which was reasonably controlled on diet and exercise alone. She did not have PIH. She did not smoke, drink alcohol, or use any recreational drugs during the pregnancy.

Discussion:

What initial investigations would you order?

What initial management would you initiate?

Case:

The CXR shows the following image. Blood gas shows 7.23/23/17/-8, CRP 20.1, lactate of 4.8. WBC 20.3, Neuts 12.3, no left shift, Hb 165, platelets 267.



## Recommendations for neonatal surfactant therapy



Canadian  
Paediatric  
Society

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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 O<sub>2</sub> 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 PCO<sub>2</sub> 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 CO<sub>2</sub> 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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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.

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# Respiratory Distress in the Term and Near-term Infant

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Drs Flidel-Ramon and Shinwell did not disclose any financial relationships relevant to this article.

**Objectives** After completing this article, readers should be able to:

1. Differentiate between cardiac and respiratory causes of cyanosis.
2. Describe the primary parenchymal diseases that can cause respiratory distress in the neonate.
3. Describe the primary developmental lung abnormalities that can cause respiratory distress in the neonate.

## Introduction

One of the most common reasons for admission of term neonates to a neonatal intensive care unit (NICU) is respiratory distress. (1) The cause may be of pulmonary or nonpulmonary origin. The nonpulmonary causes include cardiac, infectious, metabolic, central nervous system, and miscellaneous conditions. This review focuses on the major pulmonary causes for respiratory distress in term infants, in particular, the first two of the four groups that appear in Table 1. (2)

## Rule Out Cardiac Disease

Differentiating cardiac and respiratory causes of cyanosis is a common clinical problem, particularly in cases in which there is little or no tachypnea or respiratory distress. The major signs of neonatal respiratory distress are tachypnea and cyanosis, in which tachypnea is defined as a respiratory rate consistently greater than 60 breaths/min. A hyperoxia test may assist in differentiating between the two. Pulse oximetry may help to decide whether a formal hyperoxic test is useful. A neonate who exhibits cyanosis without marked respiratory distress and has an O<sub>2</sub> saturation of less than 85% in both room air and 100% oxygen likely has an intracardiac shunt. If the O<sub>2</sub> saturation increases to more than 85% on 100% oxygen, a full hyperoxia test should be performed. The test consists of obtaining a baseline right radial (preductal) arterial blood gas measurement with the child breathing room air and repeating the measurement while the infant is receiving 100% O<sub>2</sub>. A PaO<sub>2</sub> measurement greater than 300 mm Hg on 100% oxygen is normal, more than 150 mm Hg suggests pulmonary disease, and 50 to 150 mm Hg suggests cardiac disease (or severe pulmonary hypertension). (3) Echocardiography is the definitive investigation, but because it is not immediately available in most units at all hours of the day and night, it is important for the clinician to be familiar with the previously noted initial approach.

## Hints on the Chest Radiograph

For respiratory distress caused by parenchymal disorders, the standard chest radiograph remains the most common and useful imaging tool. (4) The location of the stomach, liver, and heart should be determined to rule out dextrocardia and situs inversus. The spectrum of diseases that affect the neonate's chest have significant overlap in their radiographic and clinical appearances, such that an open exchange of information between the neonatologist and radiologist is critical for intelligent interpretation of the radiologic images in conjunction with the clinical picture. The following is a brief overview of possible diagnostic clues (see also Table 2).

In term (rare) or near-term infants who have respiratory distress syndrome (RDS), the maximum radiographic findings may not be present until 24 to 48 hours after birth. The

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## Table 1. Potential Pulmonary Causes for Respiratory Distress in Neonates

### Parenchymal conditions

- Transient tachypnea of the newborn
- Meconium aspiration syndrome and other aspirations
- Respiratory distress syndrome
- Pneumonia
- Pulmonary edema
- Pulmonary hemorrhage
- Pulmonary lymphangiectasia

### Developmental abnormalities

- Lobar emphysema
- Pulmonary sequestration
- Cystic adenomatoid malformation
- Congenital diaphragmatic hernia
- Tracheoesophageal fistula
- Pulmonary hypoplasia

### Airway abnormalities

- Choanal atresia/stenosis
- Laryngeal web
- Laryngotracheomalacia or bronchomalacia
- Subglottic stenosis

### Mechanical abnormalities

- Rib cage anomalies (eg, Jeune syndrome)
- Pneumothorax
- Pneumomediastinum
- Pleural effusion
- Chylothorax

characteristic reticular granular pattern and air bronchograms may develop as the infant uses existing surfactant stores in advance of adequate endogenous production. In addition, exogenous surfactant therapy alters the natural course of the radiographic findings. Because the surfactant may not be distributed evenly throughout the lungs, areas of aerated lung may alternate with areas of unchanged RDS. In addition, surfactant can cause excessive distention of multiple acinar units, resulting in pulmonary interstitial emphysema on the chest radiograph. Although this usually resolves spontaneously, it may be a harbinger of other pulmonary air leaks, such as pneumothorax.

In neonatal pneumonia, the chest radiograph may reveal classical patchy infiltrates, but the findings also may be indistinguishable from RDS. The presence of a pleural effusion supports the diagnosis of pneumonia; it has been reported in up to 67% of cases, but essentially

never in uncomplicated RDS. Mild cardiac enlargement in the absence of cardiac anomalies also is seen more often in pneumonia than in RDS.

The radiographic findings in meconium aspiration syndrome (MAS) vary with the severity of the aspiration. The typical chest film shows patchy areas of atelectasis due to complete airway obstruction, interspersed with areas of air trapping due to partial obstruction and a one-way valve phenomenon. There is usually widespread involvement, with no particular area of the lungs being affected more often. In severe disease, there may be an almost total white-out, with only large bronchi distinguishable. Secondary pulmonary air leaks such as pneumothorax, pulmonary interstitial emphysema, or pneumomediastinum frequently are seen.

Transient tachypnea of the newborn (TTN) is characterized by the presence of diffuse parenchymal infiltrates, a “wet silhouette” around the heart, or accumulation of fluid in the various intralobar spaces that indicate increased pulmonary interstitial, alveolar, or pleural water content. The lungs usually are affected diffusely, and sometimes it may be difficult to distinguish TTN from RDS. Similarly, in some cases of TTN, a coarse interstitial pattern may appear similar to pulmonary edema or an irregular opacification may be similar to MAS or neonatal pneumonia. Transient slight cardiac enlargement may occur.

In congenital lymphangiectasia, the lungs may appear normal or exhibit a coarse interstitial infiltrate due to the distended, abnormal lymphatics. There may be generalized overinflation. Pleural effusion may be seen in lymphangiectasia and in traumatic, chylous, or hemorrhagic effusion.

## More Imaging Modalities

Computed tomography (CT) scan may be useful in confirming the presence of the lung lesions, determining the extent of the lesion, and defining the associated abnormalities. (5) Reconstructed data from CT examination displayed in either three-dimensional or multiplanar formats are particularly helpful in delineating abnormalities of the bronchi and of arterial and venous structures. (6)

Continuous sophisticated imaging techniques such as high-resolution ultrasonography and ultrafast magnetic resonance imaging enable intrauterine definition of certain lesions.

In congenital diaphragmatic hernia (CDH), two important features that determine the prognosis are herniation of the liver into the chest and the lung-to-head

**Table 2. Possible Diagnoses Related to Radiographic Features**

Radiographic Features	Possible Diagnosis
Air bronchograms	<ul style="list-style-type: none"> <li>• RDS</li> <li>• Pneumonia</li> </ul>
Diffuse parenchymal infiltrates	<ul style="list-style-type: none"> <li>• TTN</li> <li>• MAS</li> <li>• Pneumonia</li> <li>• Pulmonary lymphangiectasia</li> </ul>
Lobar consolidation	<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Lobar sequestration</li> <li>• CCAM</li> </ul>
Patchy areas alternating with emphysema	<ul style="list-style-type: none"> <li>• MAS</li> </ul>
Pleural effusion	<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Pulmonary lymphangiectasia</li> </ul>
Reticular granular pattern	<ul style="list-style-type: none"> <li>• RDS</li> <li>• Pneumonia</li> </ul>
Loss of lung volume	<ul style="list-style-type: none"> <li>• RDS</li> <li>• MAS</li> </ul>
Fluid accumulations in interlobar spaces	<ul style="list-style-type: none"> <li>• TTN</li> <li>• Pulmonary lymphangiectasia</li> </ul>
Hyperinflation	<ul style="list-style-type: none"> <li>• TTN</li> <li>• MAS</li> <li>• Pulmonary lymphangiectasia</li> </ul>
Atelectasis	<ul style="list-style-type: none"> <li>• MAS</li> <li>• RDS</li> </ul>
Pneumothorax/pneumomediastinum	<ul style="list-style-type: none"> <li>• Spontaneous</li> <li>• MAS</li> <li>• RDS</li> <li>• Pneumonia</li> </ul>
"Cystic" mass	<ul style="list-style-type: none"> <li>• CCAM</li> <li>• CDH</li> <li>• Pulmonary sequestration</li> </ul>
RDS=respiratory distress syndrome, TTN=transient tachypnea of the newborn, MAS=meconium aspiration syndrome, CCAM=congenital cystic adenomatoid malformation, CDH=congenital diaphragmatic hernia	

circumference ratio (LHR). Liver herniation may be determined sonographically by Doppler evaluation of the abnormal course of the umbilical, hepatic, and portal veins. The LHR estimates the volume of the contralateral lung, thereby providing a measure of the expected degree of pulmonary hypoplasia. When the LHR is less than 0.9, the outcome is usually poor; when it is greater than 1.4, a good outcome is more likely. (7) This information may influence parents to consider delivering at a center that has advanced therapeutic modalities, such as extracorporeal membrane oxygenation (ECMO).

Congenital lobar emphysema may be detected in utero as an echogenic mass on ultrasonography, with associated mediastinal shift and displacement of the heart resulting in compression of the contralateral lung. Fetal

ultrasonography may diagnose extralobar emphysema as early as 19 weeks of gestation. (6)

### Parenchymal Diseases

#### TTN

TTN initially was described by Avery and colleagues in 1966. (8) This relatively benign, self-limited disease also is known as RDS type 2 or wet lungs. It occurs in approximately 11 per 1,000 live births and appears more often in boys, in infants delivered by cesarean section, and in infants who have perinatal asphyxia, umbilical cord prolapse, or maternal complications such as asthma, diabetes, or analgesia or anesthesia during labor. The syndrome is characterized by tachypnea that appears shortly after birth and usually clears within 1 to 5 days. The precise cause is unknown, but it is believed to be due to delayed resorption of fetal lung fluid that may be related to elevated central venous pressure and delayed clearance of pulmonary liquid by the lymphatics. The reason for the delayed absorption is unknown, but it has been suggested to be attributed to mild asphyxia resulting in mild pulmonary capillary leak and to myocardial dysfunction with elevated filling pressure. (9) In most cases,

the clinical course is benign, and mechanical ventilation almost never is required.

#### RDS

Although RDS is primarily a disease of preterm infants, some near-term infants may be affected. These infants are typically 34 to 37 weeks of gestation, and risk factors include maternal diabetes, multiple birth, cesarean section prior to the onset of labor, perinatal asphyxia, cold stress, and infants whose siblings suffered from RDS. Because their surfactant sufficiency is borderline and they have larger pulmonary reserves, affected infants may be able to cope without ventilation for longer than smaller preterm infants. Infants who have RDS may do well with nasal continuous positive airway pressure or may require

ventilation. Surfactant often improves pulmonary mechanics significantly but has little effect on overall outcome, which is favorable in most cases. (10)

### Abnormalities of Surfactant Proteins

A small but notable group of term infants who have severe respiratory distress have congenital abnormalities of surfactant proteins. The most common of these conditions is deficiency of surfactant protein B (SP-B). Affected infants develop severe respiratory distress shortly after birth, and chest radiographs show findings identical to those of RDS. However, infants who have deficiency of SP-B continue to suffer from extreme respiratory insufficiency despite mechanical ventilation, oxygen, repeated surfactant replacement therapy, and corticosteroids. The only effective therapy (although neither available for nor consented to by all) is lung transplantation, without which the infants die within 1 to 6 months.

SP-B deficiency is transmitted as an autosomal recessive trait and is fatal in homozygotes; heterozygotes are clinically asymptomatic. Compound heterozygotes (two different mutant alleles at the same loci) have a milder form of the disease. The gene for SP-B is located on chromosome 2 and comprises 11 exons. The most common defect (60% to 70%) in the SP-B gene is a frame shift mutation caused by a base pair insertion that results in a premature stop codon that prevents translation. (11)

The typical pathology in the lung is alveolar proteinosis. Distended alveoli are filled with proteinaceous material and detached alveolar epithelial cells, and the alveolar septa are thickened. In the airways, SP-B is markedly reduced or absent and, by comparison, there are large amounts of abnormal SP-A and SP-C. Abnormal processing of SP-C results in its accumulation within type 2 pneumocytes. Ultrastructural examination reveals an absence of normal lamellar bodies and tubular myelin, which are replaced by multivesicular bodies and multilamellated structures. There also is an accumulation of lipid vesicles between the alveolar epithelium and its basement membrane. (12)

To date, no human infants who lack SP-A have been identified. Abnormalities of SP-C and SP-D have been identified but do not appear to be associated with respiratory distress in human infants.

### MAS

MAS is defined as respiratory distress in an infant born through meconium-stained amniotic fluid whose symptoms cannot otherwise be explained. Historically, many of these infants were postmature, although this is seen less often today because obstetricians rarely allow preg-

nancy to continue to more than 41 weeks' gestation. Approximately 13% of all live births are complicated by meconium-stained amniotic fluid, and of these, 4% to 5% of infants develop MAS. (13)

The mechanisms of injury include direct toxicity of the meconium causing chemical pneumonitis, inactivation of surfactant, activation of complement, and vasoconstriction as well as partial or complete airway obstruction by the thick, particulate meconium. Secondary pulmonary hypertension is a frequent associated finding.

The management of MAS remains a challenge. (14) Before delivery, the infusion of isotonic solution into the amniotic cavity via a catheter is termed amnioinfusion. Studies have shown that this intervention in pregnancies complicated by thick meconium and oligohydramnios can reduce the rate of MAS and fetal distress significantly. However, in view of significant adverse effects, this has not become an accepted therapy. (14)

Current recommendations are to perform intrapartum oropharyngeal suction before delivery of the body in all cases of meconium-stained amniotic fluid. This approach recently was challenged by a large multicenter, randomized, controlled trial that included more than 2,000 infants and showed no beneficial effect of suctioning on the incidence of MAS. (15) Results of this study may influence practice significantly. Similarly, elective intubation and tracheal suction was a standard therapy in the past, although this practice also has not withstood the test of time. Wiswell and coworkers, in their large randomized study, showed no difference in the rate of MAS in neonates who were intubated and had tracheal suctioning compared with those who were not intubated. (16) Another prospective randomized study designed to determine whether routine tracheal suctioning is indicated in all meconium-stained healthy term neonates showed that the procedure was not harmless and is unnecessary in a vigorous term neonate who has meconium-stained fluid. (17)

Because meconium is known to inactivate surfactant, exogenous replacement therapy seems logical. Randomized, controlled studies have shown that surfactant treatment reduces the need for ECMO and may reduce the risk for pneumothorax in neonates who have MAS. (18) Calf lung surfactant therapy was shown to cause significant, but short-term improvement in the oxygenation index. (19) This suggests a dose-response relationship between the surfactant inactivation and its replacement. Another method for surfactant administration in MAS is as a lavage with diluted surfactant. The use of lavage can help to remove meconium while simultaneously replacing the inactivated surfactant. (20)(21)

The use of inhaled nitric oxide (iNO) increases oxygenation in neonates who have MAS. Since the approval of iNO by the United States Food and Drug Administration in 2001, there has been a steady decrease in the use of ECMO for neonates who have MAS. (22)

Treatment of MAS has improved over the last decade with new ventilatory modalities, such as different methods of high-frequency ventilation, but no randomized trials have compared the different forms of ventilation in this setting. Experimental studies in animals have compared the use of high-frequency ventilation with conventional ventilation and have shown enhanced carbon dioxide elimination, increased lung compliance, and diminished right-to-left shunts. (14) Despite these advances, MAS remains a challenging condition with a significant mortality risk.

### Pneumonia

Pneumonia may be acquired in utero, during delivery (or perinatally), or postnatally in the nursery or at home. It may be classified as either early- (<7 d of age) or late-onset (>7 d of age).

At autopsies of both stillbirths and liveborn neonatal deaths, pneumonia was found to be present in 20% to 60% in different centers. (23)(24) The definition of the pneumonia was based on the presence of polymorphonuclear leukocytes in the alveoli or interstitium, although the presence of bacteria was not necessary for the definition.

The causative agent varies, depending on whether the infection is acquired before, during, or after birth in the nursery or at home. (24) Intrauterine infection is usually the result of maternal infection, which may be transmitted transplacentally and involves many organs (including blood, liver, central nervous system, lungs). Pathogens include rubella, cytomegalovirus, herpes simplex virus, mumps, adenovirus, *Toxoplasma gondii*, *Treponema pallidum*, *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Varicella zoster*, and human immunodeficiency virus.

Pneumonias that are acquired at birth most often are caused by group B *Streptococcus*, but *Escherichia coli*, *Klebsiella* sp, and *Chlamydia trachomatis* also are seen. *C trachomatis* pneumonia typically presents at a later age (3 wk). Pneumonias acquired after birth in the nursery or at home include those caused by respiratory viruses (adenovirus, respiratory syncytial virus), gram-positive bacteria (groups A, B, and G streptococci or *Staphylococcus aureus*), and gram-negative enteric bacteria (*Klebsiella* sp, *Proteus* sp, *Pseudomonas aeruginosa*, flavobacteria, *Serratia marcescens*, and *E coli*). (25)

Congenital pneumonia is a severe disease that frequently results in either stillbirth or death within the first 24 hours after birth. Pneumonias that are acquired later present most often as systemic disease. Management includes oxygen therapy, ventilatory support, antibiotics, and often vasopressor support such as dopamine and dobutamine.

### Lymphangiectasia

Congenital errors of lymphatic development can lead to primary pulmonary disorders that include lymphangioma, lymphangiectasia, lymphangiomatosis, and lymphatic dysplasia syndrome. (26) Because of their rarity, they often are misdiagnosed. The origins of these disorders are unknown.

Primary lymphangiectasia is a congenital disorder of the lymphatic system characterized by marked dilatation of the lymphatic vessels that leads to obstruction and leakage of fluid. (27) This is seen in the visceral pleura as well as interlobular septa and results in chylothoraces, which lead to respiratory compromise or failure. Intestinal and thoracic lymphangiectasia may occur in isolation or simultaneously in the same patient as part of a generalized lymphatic dysplasia. Primary lymphangiectasia is a rare congenital malformation, with the age of presentation ranging from in utero to early adulthood. When present in the neonatal period, the clinical course is usually fatal.

The lymphatic vascular system develops during the sixth week of fetal life as an outgrowth of the venous system or as a de novo differentiation within the mesenchymal tissue. They join one another to form the lymphatic channels. The pulmonary lymphatic channels develop before the 20th week of fetal life. Primary congenital lymphangiectasia results from failure of the pulmonary interstitial connective tissue to regress, leading to dilation of pulmonary lymphatic capillaries. The lung appears heavy and noncompliant. The visceral pleura have a network of dilated lymphatics that weep lymph fluid when sectioned. Open lung biopsy is required to make the diagnosis. Supportive therapy, including albumin infusions, diuretics, thoracentesis, and paracentesis, provide transient relief of symptoms. Dietary modifications are aimed at controlling symptoms and consequences of lymphatic obstruction but do not modify the underlying disease process. Primary pulmonary lymphangiectasia often is associated with a number of congenital and genetic diseases, including Noonan, Ullrich-Turner, Ehlers-Danlos, and Down syndromes.

## Developmental Lung Abnormalities

### CDH

CDH occurs in 1 in 2,000 to 4,000 births. Males are affected more often (male:female ratio of 1.5:1), and the recurrence risk in future pregnancies is 2%. CDH is a developmental abnormality of the diaphragm resulting in a defect that permits abdominal viscera to enter the chest. Usually the defect occurs before the eighth week of embryonic life. It is seen more often in the posterolateral segments of the diaphragm and more often on the left side. Some 95% occur through the posterior foramen of Bochdalek that lies posteriorly and lateral to the spine, and of these, 80% are on the left side. Classic thinking has been that the primary defect is in the diaphragm and that pulmonary hypoplasia is due to pressure from the abdominal viscera in the thoracic cavity. However, information based on the murine nitrofen-induced diaphragmatic hernia model suggests that proper formation of the diaphragm requires the normal formation of the lung and that pulmonary hypoplasia is the cause rather than the result of the diaphragmatic hernia. It has been shown that pulmonary hypoplasia occurs before the diaphragm is closed. (28) Cellular mechanisms that appear to be involved include altered regulation of expression of vascular endothelial growth factor and its receptor, fibroblast growth factors 7 and 10, insulin-like growth factor, and sonic hedgehog. Glucocorticoid receptor is increased, suggesting a protective role for glucocorticoids. Another protective factor appears to be retinoic acid. (29)

Despite the many advances in critical care and ventilator management, CDH continues to be an extremely challenging problem in the NICU. The morbidity and mortality remain high and are related primarily to pulmonary hypoplasia and pulmonary hypertension. In the delivery room, the neonate typically presents with respiratory distress shortly after birth. Physical examination may show the abdomen to be scaphoid. Air entry is reduced on the affected side, and the heart sounds are displaced. Immediate treatment includes intubation and mechanical ventilation, and a nasogastric tube should be passed for decompression. Bag-and-mask ventilation should be avoided to prevent gastric dilatation that may compromise pulmonary function further. New approaches to managing CDH that have been explored include the use of extracorporeal life support (ECMO), high-frequency ventilation, delayed surgical repair, permissive hypercapnia, nitric oxide, surfactant administration, intratracheal pulmonary ventilation, and liquid ventilation. (30) Despite the new approaches, mortality rates remain high, ranging from 25% to 74% in different

reports. The presence of associated major malformations increases the mortality markedly, as does liver herniation noted at surgery. If there are no other anomalies and the defect is not part of a genetic syndrome, the prognosis after neonatal surgical repair usually is good, with overall survival rates for liveborn infants of 60% to 80%.

### Congenital Cystic Adenomatoid Malformation (CCAM)

CCAM consists of a multicystic mass of dilated bronchiole-like spaces that proliferate at the expense of alveoli. The result is the formation of a rubbery lesion that enlarges following air and fluid trapping. The cause is related to an abnormal signaling or conjugation between the developing terminal bronchioles and the alveolar mesenchyme.

Males and females are affected equally. Approximately 50% of the cases present as life-threatening respiratory distress in the neonatal period. The condition is more common on the right side, and usually only one lobe is involved. (31)

CCAM is categorized into four types. Type 1 is characterized by a small number of large cysts and is the most common (75%). In type 2, there are evenly spaced cysts that are less 1 cm in diameter. This type is associated with other congenital anomalies and poor outcome. Type 3 is rare and appears more solid on gross examination. (32) A fourth type has been defined that is characterized by acinar-type epithelium rather than the bronchiolar epithelium seen in the other three types.

At the cellular level, there is accelerated cell proliferation, with a low apoptotic index. Dysregulation of the mesenchymal growth factor, platelet-derived growth factor BB, gene expression has been implicated in the pathogenesis. (28)

Treatment is by surgical resection of the lesion. The survival rate has been reported to be 100% in neonates who do not have hydrops fetalis, but is much lower in those who have hydrops.

### Congenital Lobar Emphysema (CLE)

CLE is characterized by air trapping and overdistention of segments and lobes of the lungs. It usually is diagnosed postnatally, and 50% of the cases present by the age of 6 months. Clinical symptoms include respiratory distress, mediastinal shift, and wheezing due to spontaneous overinflation of the affected areas. The upper lobes are involved in 90% of the cases. The diagnosis can be made by simple chest radiograph, but prenatal diagnosis can be made by high-resolution ultrasonography, magnetic resonance imaging, or CT. In cases that involve

respiratory distress, the affected area should be removed. Because there are reports of spontaneous resolution, asymptomatic cases may be followed expectantly. CLE accounts for 50% of structural lesions causing respiratory distress in the newborn. It is more common in males (2:1). Sometimes the lesion can be mistaken for pneumothorax or CDH. There are associated anomalies in 14% to 40% of cases, most of which are cardiovascular. (31)(33) The prognosis is favorable, but depends on the associated abnormalities.

### Pulmonary Sequestration

Lobar sequestration is composed of abnormal lung tissue that has no connection with the normal tracheobronchial tree. There are two types of lesions, and both receive their arterial blood supply from the systemic circulation, usually a branch of the aorta.

With extralobar sequestration, the discrete mass of pulmonary parenchyma is outside the pleural investment of the lung. The lesion is found on the left side, proximal to the esophagus and between the lower lobe and the diaphragm in 66% of the cases. In 80% of the cases, the blood supply derives from the descending thoracic or abdominal aorta, and the venous drainage is to the azygous or hemiazygous vein (80%) and the rest to the pulmonary venous system. It is more common in males (3 to 4 times), and 50% of patients have respiratory distress due to compression of the rest of the lung parenchyma. In more than 65% of cases, there are associated anomalies, including CDH (20% to 30%), pericardial defects, and total anomalous pulmonary venous return.

Abnormal expression of the homeobox gene *Hoxb-5*, which is necessary for normal airway branching and development, has been implicated in the etiology. (34)

Intralobar sequestration is characterized by the lesion resting within the lobe of the lung without separate pleura. It is usually in the lower lobe (95%), and in 55% of cases is on the left side. The arterial supply comes from the abdominal aorta or celiac axis, and there may be multiple feeding arteries. The venous drainage is through the pulmonary vein. Intralobar sequestration is three to six times more common than extralobar sequestration and can be an acquired lesion that results from recurrent infection. In both types, the definitive treatment is resection of the lesion. (31)(33)

### Summary

Although most term infants who have respiratory distress have either TTN or infection, the differential diagnosis is

extensive, and the rarer causes need to be considered in atypical circumstances.

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## NeoReviews Quiz

9. A newborn is delivered at an estimated gestational age of 36 weeks by emergent cesarean section for fetal distress. The maternal history is significant for prolonged rupture of membranes. The infant has evidence of respiratory distress, and the chest radiograph shows patchy infiltrates and pleural effusion, as indicated by obliteration of both costophrenic angles. Of the following, the *most* likely cause of these chest radiographic findings in this infant is:
- A. Hyaline membrane disease.
  - B. Meconium aspiration syndrome.
  - C. Neonatal pneumonia.
  - D. Pulmonary edema.
  - E. Pulmonary hemorrhage.
10. A rare cause of respiratory distress among term newborns is a congenital abnormality of surfactant proteins. The most common of these conditions is deficiency of surfactant protein B (SP-B). Of the following, the *most* accurate statement regarding SP-B is that:
- A. SP-B deficiency is accompanied by reductions in SP-A and SP-C in airways.
  - B. SP-B deficiency is transmitted as an autosomal dominant trait.
  - C. The gene for SP-B is located on chromosome 22.
  - D. The most common defect in SP-B deficiency is a frame shift mutation.
  - E. The typical pathologic finding in SP-B deficiency is generalized alveolar atelectasis.
11. Several developmental abnormalities of lung structure can cause respiratory distress in the newborn. Of the following, the *most* common structural lesion that can cause respiratory distress in the newborn is:
- A. Congenital cystic adenomatoid malformation.
  - B. Congenital lobar emphysema.
  - C. Primary pulmonary lymphangiectasia.
  - D. Pulmonary hypoplasia.
  - E. Pulmonary sequestration.

## Respiratory Distress in the Term and Near-term Infant

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# Core Concepts: Respiratory Distress Syndrome

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Drs Warren and  
Anderson have  
disclosed no financial  
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**Objectives** After completing this article, readers should be able to:

1. Define respiratory distress syndrome (RDS).
2. Discuss the epidemiology, pathophysiology, and diagnosis of RDS.
3. Create a differential diagnosis for respiratory distress in the neonate.
4. Describe the proven treatments for RDS, with particular attention to antenatal steroids and surfactant replacement therapy (SRT), their benefits and possible complications.
5. Discuss ventilation strategies that can be used in the infant who has RDS.
6. Describe long-term complications of RDS and its treatments.

## Abstract

Respiratory distress syndrome (RDS) is seen primarily in the preterm neonate and is due mostly to pulmonary surfactant deficiency. Lung atelectasis leads to ventilation-perfusion mismatching, hypoxia, and eventual respiratory failure in the untreated infant who has RDS. RDS is diagnosed by physical findings consistent with respiratory distress and characteristic radiographic findings. Treatment of RDS begins antenatally with the administration of maternal steroids to women at risk of preterm delivery between 24 and 34 weeks' gestation. The use of repeat doses of antenatal steroids is under investigation but is currently not recommended outside of randomized, controlled trials. SRT has been approved for use since 1990 and has been successful in decreasing rates of RDS. Natural surfactant is currently recommended for use, but synthetic surfactant that contains proteins to mimic surfactant proteins is being investigated. In general, prophylactic use of surfactant is recommended over rescue treatment in infants at high risk for developing RDS, but the determination of which infants are at high risk for developing RDS remains a clinical one. The push toward use of less invasive ventilation strategies in the treatment of RDS has led to several trials of nasal continuous positive airway pressure (nCPAP). Results of the SUPPORT trial are pending, but the COIN trial has concluded that nCPAP use in infants who have RDS is not detrimental. Inhaled nitric oxide for RDS still requires investigation on safety and efficacy. Several other treatments have been studied, but as of yet, only inositol administration shows promise in the treatment of RDS. Several complications of the recommended treatments for RDS have been identified, but the benefits far outweigh the risks. Finally, there remains a need for long-term follow-up studies on preterm infants treated for RDS to assess neurodevelopmental outcomes.

## Definition

RDS, formerly known as hyaline membrane disease, occurs in incompletely developed lungs and is, therefore, a disease of prematurity. Immature lungs are functionally deficient in mature surfactant. (1) The absence of surfactant in the liquid film lining of alveoli causes an increase in surface tension and alveolar collapse. (2) If not treated, such atelectasis causes an increased work of breathing, intrapulmonary shunting, ventilation-perfusion mismatch, hypoxia, and eventual respiratory failure. (1)

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## Epidemiology

RDS is seen almost exclusively in preterm infants, before the lungs begin to manufacture adequate amounts of surfactant. (2) In fact, the risk of RDS decreases with increasing gestational age: 60% of babies born at fewer than 28 weeks' gestation, 30% of babies born between 28 and 34 weeks' gestation, and fewer than 5% of babies born after 34 weeks' gestation develop RDS. (3) Other factors that increase the risk of RDS include male sex, maternal gestational diabetes, perinatal asphyxia, hypothermia, and multiple gestations. (4) Antenatal steroids and prolonged rupture of membranes decrease the risk of RDS. (5) With the advent of therapies for RDS, including antenatal steroids and SRT, mortality from RDS has decreased from nearly 100% to less than 10% in recent years. (6)

## Differential Diagnosis

The differential diagnosis of respiratory distress in the newborn encompasses upper respiratory obstruction, pulmonary disease, cardiac disease, thoracic causes, metabolic disorders, diaphragmatic causes, neuromuscular diseases, infectious causes, hemolytic/vascular causes, and miscellaneous causes (Table 1). (7)(8)

## Pathophysiology

### Normal Lung Development

The period of viability begins at around 23 weeks' gestation, when the fetal lung begins to transition from the canalicular to the saccular stage of development (Table 2). (9) During the saccular stage, peripheral airways

enlarge and distal airways begin to dilate while their walls begin to thin. (10) Type II pneumocytes, the cells responsible for surfactant production, are present and maturing. (10) Although gas exchange is possible during this stage, total surface area for gas exchange is low and diffusion distance for gas exchange is high in relation to body weight and metabolic rate. (9) Secondary septation, or alveolarization, begins at about 32 weeks' gestation. (9) During this phase, alveoli form and mature and alveolar walls thin. (10) All cell types proliferate during this phase, including type II pneumocytes. (10) The overall result is a maturing lung with a larger surface area and a minimal diffusion distance for gas exchange. (10)

### Surfactant Composition and Life Cycle

Surfactant is a mixture of phospholipids and proteins. (2) The most abundant surface-active phospholipid in mature lungs is phosphatidylcholine. (11) Phosphatidylcholine forms a monolayer on the liquid film lining of the alveolus, lowering the surface tension of that film. (2) In addition to phospholipids, surfactant contains four major proteins: surfactant proteins (SPs) A, B, C, and D (Table 3). (11) SP-A helps to regulate surfactant secretion and uptake; SP-B and SP-C facilitate adsorption and spreading of phospholipids on the liquid film lining of the alveoli. (2) SP-D may play a role in surfactant reuptake and recycling. (5)

Pulmonary surfactant is manufactured in the Golgi apparatus and stored in lamellar bodies of type II pneumocytes. (5) Once secreted by the lamellar bodies into the extracellular space, surfactant is organized into tubular myelin, adsorbed into the air-water interface, and formed into a lipid monolayer. (5)(6) The surface-active properties of the lipid monolayer decrease the surface tension of the air-water interface and prevent alveolar collapse. (6) The majority of surfactant constituents are believed to be recycled, either through reuptake by type II pneumocytes or by alveolar macrophages. (9)

### RDS

An infant born before the alveolarization stage of lung development has underdevelopment of alveolar sacs and difficulty with oxygenation and ventilation. (9) Similarly, an infant born before this stage of lung development experiences a delay in production and secretion of functional surfactant. (9) Such surfactant deficiency is the major reason for poor lung function in the preterm neonate (Table 4). (2)

Although the preterm neonate does produce a small amount of surfactant, this surfactant contains low amounts of phospholipids and SPs. (9) It is estimated

## Abbreviations

<b>AT:</b>	antithrombin
<b>BPD:</b>	bronchopulmonary dysplasia
<b>CLD:</b>	chronic lung disease
<b>FRC:</b>	functional residual capacity
<b>GBS:</b>	group B <i>Streptococcus</i>
<b>iNO:</b>	inhaled nitric oxide
<b>IVH:</b>	intraventricular hemorrhage
<b>nCPAP:</b>	nasal continuous positive airway pressure
<b>NIH:</b>	National Institutes of Health
<b>NIMV:</b>	nasal intermittent mandatory ventilation
<b>PIE:</b>	pulmonary interstitial emphysema
<b>PVL:</b>	periventricular leukomalacia
<b>RDS:</b>	respiratory distress syndrome
<b>SP:</b>	surfactant protein
<b>SRT:</b>	surfactant replacement therapy

**Table 1. Differential Diagnosis of Respiratory Distress in the Newborn**

#### Upper Airway Obstruction

Choanal atresia, nasal stenosis, Pierre Robin sequence, laryngeal stenosis or atresia, hemangioma, vocal cord paralysis, vascular rings, tracheobronchial stenosis, masses, cleft palate, nasal stuffiness

#### Pulmonary Diseases

Respiratory distress syndrome, retained fetal lung liquid syndrome (transient tachypnea of the newborn), aspiration (including meconium aspiration syndrome), pneumonia, pneumothorax, pneumomediastinum, primary pulmonary hypertension, tracheoesophageal fistula, pulmonary hemorrhage, pulmonary hypoplasia, pulmonary agenesis, cystic disease, pleural effusion, chylothorax, neoplasm, bronchopulmonary sequestration, pulmonary arteriovenous malformation, pulmonary interstitial emphysema, pulmonary edema, congenital alveolar proteinosis, congenital lobar emphysema

#### Cardiac Diseases

Cyanotic congenital heart disease, acyanotic congenital heart disease, arrhythmia, increased intravascular volume, high output failure, pneumopericardium, cardiomyopathy

#### Thoracic Causes

Chest wall deformity, mass

#### Metabolic Disorders

Hypoglycemia, infant of a diabetic mother, inborn errors of metabolism

#### Diaphragmatic Causes

Hernia, paralysis

#### Neuromuscular Diseases

Central nervous system damage (birth trauma, hemorrhage), medication (maternal sedation, narcotic withdrawal), muscular disease (myasthenia gravis), intraventricular hemorrhage, meningitis, hypoxic-ischemic encephalopathy, seizure disorder, obstructed hydrocephalus, infantile botulism, spinal cord injury

#### Infectious Causes

Sepsis, pneumonia (especially group B *Streptococcus*)

#### Hemolytic/vascular Causes

Anemia, polycythemia, abnormal hemoglobin

#### Miscellaneous Causes

Asphyxia, acidosis, hypo/hyperthermia, hypo/hyponatremia

inadequate FRC, lung injury can occur. (9) Lung injury leads to protein exudation and edema, which can inactivate surfactant further. The acidosis and hypoxia that results from atelectasis and lung injury further interferes with surfactant production. The combination of these events leads to respiratory failure.

## Diagnosis

### Clinical Evaluation

RDS presents at the time of or soon after birth, and symptoms worsen over time. (2) Clinical symptoms of RDS are the same as those of any other respiratory distress: tachypnea, nasal flaring, chest wall retractions, expiratory grunting, and central cyanosis. (2) In the extremely preterm infant, the only clinical symptom of RDS may be apnea. (2) It is important to remember that some infants who have RDS exhibit all of these symptoms, and others may show none.

An accurate history is important in diagnosing RDS. As stated, RDS is more prevalent in earlier gestational ages, so an accurate estimation of gestational age is necessary. Other historical factors must be discerned, such as antenatal steroid therapy; maternal history of gestational diabetes; course of labor, including prolonged rupture of membranes, maternal fever, group B *Streptococcus* (GBS) status and antibiotic therapy; method of delivery; and need for resuscitation.

### Diagnostic Studies

Along with the history and physical examination, a chest radiograph is needed for the diagnosis of RDS. The typical chest radiograph shows diffuse atelectasis and the classic “ground glass” appearance of the lung fields (Figure). (2) Air bronchograms, which are air-filled bronchi superimposed on the relatively airless parenchyma of the lung tissue, also are seen commonly on chest radiograph. (2) Importantly, the appearance of GBS pneumonia on

that infants who have RDS have surfactant pools of less than 10 mg/kg compared with pools of up to 100 mg/kg in term infants. Such surfactant deficiency necessitates increased work of breathing to distend alveoli, which the preterm neonate may not be able to provide. (2) Diffuse atelectasis ensues and leads to an overall decrease in functional residual capacity (FRC) of the lungs. (2) If an infant is allowed to breathe from an

Table 2. Normal Lung Development (10)

Phase	Embryonic	Pseudoglandular	Canalicular	Saccular	Alveolar
Gestation (weeks)	~0 to 7	~7 to 17	~17 to 27	~28 to 36	~36+
Structures	Trachea and bronchi	Conducting airways and terminal bronchioles	Respiratory bronchioles, alveolar ducts, primitive alveoli	Enlarged peripheral airways, thinned alveolar walls	Definitive alveoli
Type II Pneumocytes	Absent	Immature; undifferentiated	Immature; differentiated	Developing laminar bodies	Mature

chest radiograph can be identical to that of RDS. (12) Empiric antibiotics to address GBS infection should be started until such disease is ruled out. Arterial blood gas measurements show hypercarbia and hypoxia and eventually, in the unsupported infant, metabolic acidosis. (2) In all, a preterm infant must have clinical signs of respiratory distress and a classic chest radiograph to be diagnosed with RDS. (2)

### Management

#### Antenatal Steroids

Antenatal steroid administration to women at high risk of preterm delivery prior to 34 weeks' gestation has been standard of care since the 1994 National Institutes of Health (NIH) Consensus Conference. (13) A Cochrane review by Roberts and Dalziel from 2006 confirmed the benefits of antenatal steroids, which include decreases in neonatal death, intraventricular hemorrhage (IVH), and RDS. (1) Antenatal steroids are believed to decrease the incidence of RDS by accelerating maturation of the fetal lung. (13)

Early studies on the use of antenatal steroids did not include data on babies who were delivered before

28 weeks' gestation, so there was a question of whether antenatal steroids would be beneficial in this age group. The Roberts and Dalziel review shows that when steroids are administered initially at 26 weeks' gestation, there is a decreased incidence of RDS that is not seen if steroids are administered before 26 weeks' gestation. (1) However, the incidence of IVH still may be reduced if steroids are administered at fewer than 26 weeks' gestation. (1) Therefore, because of the apparent benefit to preterm infants in terms of decreased IVH, antenatal corticosteroid administration is recommended for preterm infants starting at 24 weeks' gestation. (13)

Both betamethasone and dexamethasone have been studied and found to be more effective than placebo, but these steroids have not been examined head-to-head. (13) The Roberts and Dalziel review suggests that betamethasone may cause a larger reduction in RDS than dexamethasone. (1) Baud and colleagues (14) found that antenatal exposure to betamethasone, but not dexamethasone, is associated with a decreased risk of periventricular leukomalacia (PVL) in preterm infants, but there is no difference in the incidence of cerebral palsy. (1) With this limited evidence, two doses of betamethasone administered 24 hours apart is currently the recommended steroid for antenatal use. (13)

Antenatal steroid administration has been shown to be beneficial if provided fewer than 24 hours before

Table 3. Surfactant Proteins and Their Functions (5)

Surfactant Proteins	Functions
SP-A	Part of the host innate immune defense Facilitates the formation of tubular myelin Regulates surfactant secretion and uptake
SP-B	Promotes adsorption and spreading of pulmonary surfactant
SP-C	Promotes adsorption and spreading of pulmonary surfactant
SP-D	Part of the host innate immune defense May play a role in pulmonary surfactant reuptake and recycling

Table 4. Results of Surfactant Deficiency (2)

1. Decreased lung compliance
2. Unstable alveoli
3. Decreased functional residual capacity
4. Hypoxia (from shunting of blood through atelectatic portions of the lung)
5. Increased work of breathing
6. Lung edema (exudation of fluid and serum proteins)



Figure. Classic chest radiograph in an infant who has RDS.

delivery. Therefore, steroid administration is recommended before delivery of preterm infants 24 to 34 weeks' gestation unless delivery is imminent. (13) Furthermore, a reduction in RDS has been seen in infants born up to 7 days after the first dose of antenatal steroids was administered. (1) No benefit is seen in infants who receive the first dose of steroids more than 7 days before birth. (1)

Because antenatal steroids seem to be of benefit only when administered from just before birth to 7 days before delivery, the utility of repeated antenatal steroid dosing has been studied. The latest Cochrane review on the subject, conducted by Crowther and Harding in 2007, suggests that repeat doses of prenatal steroids do reduce the incidence and severity of neonatal lung disease in the first few postnatal weeks. (15) They recommend repeat doses of corticosteroids in women at risk for preterm birth when the first course of steroids was administered more than 7 days previously because of the short-term benefits to the fetal lungs. They do, however, warn about the possibility of decreased birthweight and head circumference at birth, which has been reported. For example, repeat antenatal steroid courses in fetal sheep result in increased lung maturation as well as increased growth restriction. (13) Guinn and colleagues

(16) showed that the composite neonatal morbidity, including severe RDS, bronchopulmonary dysplasia (BPD), severe IVH, PVL, sepsis, necrotizing enterocolitis, or perinatal death, was not reduced by using weekly courses as compared with one course of antenatal steroids. Because the true risk-to-benefit ratio of using repeat doses of antenatal steroids is not known, the 1994 and 2000 NIH Consensus Conference recommends the use of repetitive courses of steroids only in the context of randomized, controlled trials (Table 5). (13)

### Surfactant

SRT was approved for use by the United States Food and Drug Administration in 1990. (5) Immediate improvement in oxygenation, along with improved aeration on chest radiograph within 1 hour, is seen after administration of SRT. (5)(17) SRT reduces the incidence of RDS, death, pneumothorax, pulmonary interstitial emphysema (PIE), and IVH in preterm infants. (17) Although most available evidence suggests that SRT increases survival rates without increasing the risk of disability, the risk of long-term disability is unknown due to few reported

### Table 5. Summary of 1994 and 2000 National Institutes of Health Consensus Conference Antenatal Steroid Recommendations

1. The benefits of prenatal corticosteroids outweigh any risks that have been identified. The benefits include decreased death and decreased incidence of respiratory distress syndrome and intraventricular hemorrhage.
2. All fetuses at 24 to 34 weeks' gestation are candidates for corticosteroid therapy.
3. Prenatal corticosteroid therapy should be used without consideration of fetal sex, race, or the availability of surfactant treatments for respiratory distress syndrome.
4. Prenatal corticosteroids should be administered if tocolytics are used.
5. Because of probable benefit for treatment to delivery intervals of less than 24 hours, prenatal corticosteroids are indicated unless delivery is imminent.
6. Repeated courses of corticosteroids may not be safe and should not be administered outside of clinical trials.

Reprinted with permission from Jobe. (13)

follow-up studies on the preterm infants who have received surfactant. (17)

Surfactant is administered directly into the lungs via an endotracheal tube. (5) Other methods of surfactant administration, including aerosolization, nebulization, and instillation via bronchoalveolar lavage, have been found to be ineffective. (5) Surfactant administration via laryngeal mask airway is being studied. (5) Surfactant can be administered as either two or four fractional doses in either two or four different body positions; clinical evidence is not sufficient to recommend an optimal number of fractional doses. (17) Surfactant can be administered as either a bolus or an infusion into the endotracheal tube; again, data in humans are insufficient to recommend an optimal method of surfactant administration. (17) Interestingly, data examining the distribution of surfactant in mechanically ventilated rabbits showed that bolus instillation resulted in reasonably homogenous pulmonary surfactant distribution, while tracheal infusion resulted in extremely uneven pulmonary distribution. (18)

Natural and synthetic surfactant preparations exist, and both are effective in the treatment and prevention of RDS. (19) Natural surfactants are derived from animal lungs (bovine or porcine) and contain phospholipids with SP-B and SP-C; first-generation synthetic surfactants contain only phospholipids without proteins. (19) A Cochrane meta-analysis by Soll and Blanco conducted in 2001 comparing natural surfactant to first-generation synthetic surfactant confirmed that natural surfactant more effectively reduces the risk of pneumothorax and lowers mortality rates in infants treated for RDS. (20) There is also a marginal decrease in the risk of BPD when using natural surfactant. Although natural surfactants appear to be associated with higher rates of IVH, grade 3 and 4 IVH rates are not increased. The conclusion of this meta-analysis is that natural surfactants are the more desirable choice over the first-generation synthetic surfactants, which is likely due to the inclusion of the SPs in the natural surfactant. (20)

Synthetic surfactants containing peptides that mimic SPs recently have been developed and tested. (21) In a meta-analysis of two studies comparing protein-containing synthetic surfactant to natural surfactant, no statistically significant differences were found between the two groups in terms of death or chronic lung disease (CLD), and clinical outcomes were generally similar. (21) Further studies comparing these two groups are needed.

The use of prophylactic versus selective administration of surfactant has been studied thoroughly. Prophylactic SRT involves intubation and surfactant administra-

tion in preterm infants at high risk for RDS and usually occurs after the initial resuscitation and within 10 to 30 minutes of birth. (17) Prophylactic SRT has the advantage of establishing a normal surfactant pool before damage due to a low FRC, and an increased work of breathing can occur. (5) Its major disadvantage is the possibility that an infant who would not have developed RDS may be intubated and treated with surfactant. (5) Selective, or rescue, SRT is the administration of surfactant to preterm infants who already have developed RDS. (17) The two types of selective SRT are early and late. (17) Early selective SRT is administered within 1 to 2 hours of birth; late selective SRT occurs 2 or more hours after birth. The advantage of selective SRT is the avoidance of overtreatment, but in those infants who develop RDS, the delay in treatment allows lung inflammation and damage to occur. (5)

In the Cochrane review by Soll and Morley in 2001, the use of prophylactic surfactant in infants at high risk of developing RDS was compared with selective surfactant treatment at the time of respiratory failure. (22) Prophylactic surfactant treatment was associated with a significant reduction in the risk of pneumothorax, PIE, mortality, and BPD or death. (22) A secondary analysis of infants of fewer than 30 weeks' gestation found a significant decrease in the risk of mortality and the risk of BPD or death. The conclusion of this study is that prophylactic surfactant is beneficial in preterm infants believed to be at high risk for developing RDS, but the best method of determining if an infant is at high risk for developing RDS remains unclear. (22)

Because the incidence of RDS decreases with increasing gestational age, it becomes likely that prophylactic treatment with surfactant once gestational ages approach 28 to 30 weeks results in a good percentage of overtreatment. (5) In these cases, it may make more sense to treat selectively with surfactant. The most recent Cochrane review examining early versus late selective surfactant administration found that early selective SRT decreased neonatal mortality, pneumothoraces, PIE, and the incidence of CLD and death at 36 weeks' postmenstrual age when compared with late selective SRT. (5)

Finally, in 1999, a Cochrane review compared multiple versus single doses of natural surfactant for the treatment of RDS. (23) The reason for this comparison was the observation that some infants seemed to relapse after initial surfactant treatment. In this meta-analysis, a more sustained response in the treatment of RDS was seen in the group of infants allowed to have multiple doses of surfactant. (23) A decreased risk of pneumotho-

rax and a trend toward a decreased risk of mortality also was reported.

Overall, survival without BPD has increased since SRT began, although the incidence of BPD in very low-birthweight infants is unchanged. (17) The risk of respiratory problems later in infancy or childhood (including asthma and infection) remains high for preterm infants who were treated with surfactant and mechanical ventilation. (17) Long-term studies are needed to assess the respiratory function of children who received surfactant as preterm infants. (17)

### Antenatal Steroids and Surfactant

No randomized, controlled trials have been conducted to address whether antenatal steroids reduce the need for prophylactic or rescue SRT in preterm infants. (17) On subgroup analyses of observational studies and clinical trials, infants born before 32 weeks' gestation who received both antenatal steroids and SRT had significant reductions in mortality, severity of respiratory distress, and frequency of air leaks compared with infants who received neither treatment, only antenatal steroids, or only SRT. (17) Infants born before 27 weeks' gestation did not have a lower incidence of RDS, but the severity of RDS may have been decreased. Therefore, it is generally accepted that the effects of antenatal steroids and SRT are additive, and it is not expected that trials will be conducted to verify this.

### Ventilatory Management

Several methods can be used to ventilate the preterm neonate at risk for RDS. Surfactant administration followed by conventional ventilation has historically been the management of choice, but concerns that both positive pressure ventilation via the endotracheal tube and the duration of mechanical ventilation have direct effects on the incidence of BPD have prompted investigators to search for less harsh ventilatory strategies. (24)(25) Because most preterm infants who have RDS require ventilatory support and BPD is a major morbidity of many forms of ventilatory support, the hope is to find a noninvasive method of ventilation for RDS that is both safe and effective.

The initial belief was that more complex ventilation strategies, such as high-frequency oscillatory ventilation, might decrease the risk of developing BPD. However, when optimal lung volume strategies are used, there is no difference between conventional ventilators and high-frequency ventilators in terms of pulmonary and nonpulmonary outcomes. (24)(25) A Cochrane review on this

subject from 2007 confirmed the lack of clear evidence for elective use of high-frequency ventilation over conventional ventilation because no difference was documented in mortality between the two modes of ventilation at 30 days or at term-equivalent age. (26) Patient-triggered ventilation is a form of conventional ventilation that includes synchronized intermittent mandatory ventilation, assist control, and pressure support. (24)(25) Studies have shown that patient-triggered ventilation has benefits over conventional ventilation and high-frequency ventilation in terms of a decreased duration of mechanical ventilation and decreased number of days on oxygen. (24)(25) However, there was no significant difference in terms of a decrease in lung injury between the three ventilation strategies.

The noninvasive ventilation strategy of nCPAP is believed to work by improving oxygenation without increasing PaCO<sub>2</sub> through the stabilization and recruitment of collapsed alveoli. (27) The idea is that nCPAP will help to achieve the adequate FRC that is necessary to avoid the development of RDS because increased FRC means increased alveolar surface area and less intrapulmonary shunt. (27) The avoidance of endotracheal intubation saves the infant from the barotrauma and volutrauma seen with the use of mechanical ventilators. A Cochrane Review from 2002 states that although a higher rate of pneumothorax was seen, there was an overall reduction in respiratory failure and mortality in preterm infants who had RDS and were treated with nCPAP. (28) Large randomized, controlled trials to evaluate this possibility are underway.

The COIN trial (Continuous Positive Airway Pressure or Intubation at Birth) is a recently published randomized trial addressing whether the use of nCPAP shortly after birth would decrease the rates of death and BPD (defined as the need for oxygen at 36 weeks gestational age). (29) A total of 610 infants from gestational ages 25 to 28 and 6/7 weeks were randomized at 5 minutes after birth to receive either nCPAP or intubation and mechanical ventilation. Outcomes between the two groups were assessed at 28 days, 36 weeks gestational age, and before discharge. There was a significantly lower risk of death or need for oxygen at 28 days in the nCPAP-treated infants, but early nCPAP did not significantly decrease the rates of death or BPD compared with intubation and ventilation at 36 weeks gestational age. Infants in the nCPAP group required fewer overall days of ventilation, but also had a significant increase in pneumothoraces compared with mechanically ventilated infants. The overall conclusion of the study was that early

nCPAP was not detrimental to preterm infants whose gestational ages were between 25 and 28 and 6/7 weeks. (29)

The SUPPORT trial (Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birthweight Infants) is currently ongoing. This trial is randomizing infants of gestational ages between 24 weeks and 27 and 6/7 weeks to either a treatment group of CPAP and permissive ventilation management or a control group of prophylactic/early surfactant and conventional ventilator management as well as either a low (85% to 89%) or high (91% to 95%) SpO<sub>2</sub> group. Results of this study are pending. (30)

Finally, nasal intermittent mandatory ventilation (NIMV) has been studied in the treatment of RDS. The rationale for NIMV use is that the administration of “sighs” to the neonate can help to open microatelectasis and recruit more alveoli. (31) Kugelman and associates (31) showed that NIMV was more successful than nCPAP in the initial treatment of RDS among infants younger than 35 weeks’ gestation by reducing the rate of endotracheal intubation and the incidence of BPD. (31) As with other studies, failure of nasal respiratory support was associated with lower birthweight. Further study is needed, but NIMV may be a promising non-invasive method of ventilation for preterm infants at risk for RDS.

### Ventilatory Management and Surfactant

Surfactant is a proven treatment for RDS that must be administered via endotracheal tube. As ventilation strategies become more sophisticated and less invasive, the use of surfactant may become more complicated. The push toward less invasive ventilation strategies does not allow an opportunity for surfactant administration. To allow for use of surfactant, many centers have started to intubate, administer surfactant, and extubate to minimally invasive respiratory support (“in-and-out surf”). A recent Cochrane Review compared early surfactant administration with brief ventilation to selective surfactant with continued mechanical ventilation in preterm infants who had or were at risk for RDS. (32) The use of surfactant followed by early extubation to nCPAP was more effective than selective intubation and surfactant administration followed by mechanical ventilation in preventing the need for mechanical ventilation as well as decreasing the incidence of BPD and pneumothorax. (32) No investigators currently are examining the use of early and continuous nCPAP versus surfactant administration followed by early extubation and nCPAP.

### Inhaled Nitric Oxide (iNO)

NO is a vascular endothelial relaxing factor that successfully causes local smooth muscle cell relaxation in the pulmonary circulation when delivered by inhalation. (33) iNO has been used as a treatment in illnesses in which pulmonary vasodilation would be of benefit. Pulmonary hypertension is recognized as a complicating factor that may contribute to RDS. (33) The ability of iNO to dilate the blood vessels in the pulmonary vasculature, reduce pulmonary hypertension, and improve ventilation-perfusion matching (a known problem in RDS) has led to clinical trials on the use of iNO in the preterm infant who has RDS. (33) Of note, one major concern for the use of iNO in preterm infants is the adverse effect of bleeding complications.

In the Cochrane Review conducted by Barrington and Finer in 2007, iNO possibly improved outcome in mildly ill infants, with a possible decrease in ICH. (34) However, when administered to very ill preterm infants, iNO did not improve outcome and may have contributed to an increase in ICH. (34) Overall, the benefit of iNO in the preterm infant is largely unknown, and further randomized, controlled trials with subsequent meta-analyses are needed to answer this question. (33)

### Other

Several other therapies have been studied as possible treatments for RDS. The following therapies have been reviewed in meta-analyses and published in the Cochrane Database of Systematic Reviews.

**DIURETICS.** RDS may be complicated by lung edema, so studies have been performed to determine if administration of diuretics may improve the course of RDS. A Cochrane Review by Brion and Soll in 2007 (35) analyzed seven studies with the aim of assessing risks and benefits of diuretic use in preterm infants who had RDS. Six of these studies used furosemide and were conducted before the era of prenatal steroids and surfactant. Although a transient furosemide-induced improvement in pulmonary function was seen, this benefit did not outweigh the risk for patent ductus arteriosus and hemodynamic instability. There were no long-term benefits. The other study assessed theophylline use and found no long-term benefits. Overall, the reviewers of these studies did not find data to support the routine administration of furosemide or theophylline in preterm infants who had RDS. (35)

**ANTITHROMBIN (AT).** AT is produced by the liver and is important in both blood clotting and clot lysis. Infants

who have RDS, as well as infants who have other critical illnesses, have low serum AT concentrations. It was hypothesized that increased thrombin formation due to low AT concentrations might contribute to the pathophysiology of RDS and that administration of AT may improve the clinical course of affected infants. A review by Bassler and associates (36) found a trend toward increased mortality as well as a significantly prolonged duration of mechanical ventilation and oxygen therapy in the AT-treated group. Therefore, due to the lack of benefit, as well as the potential harm, AT is not a recommended treatment for infants who have RDS.

**DIGOXIN.** It has been suggested that pulmonary edema due to congestive heart failure may contribute to RDS in the neonate. Based on this suggestion, digoxin has been studied as a potential treatment in RDS. Two randomized, controlled trials were analyzed by Soll, (37) who found that digoxin did not result in improved RDS symptoms. Therefore, digoxin is not recommended for use in infants solely affected with RDS.

**INOSITOL.** Inositol is a nutrient required by cells for growth and survival that also has been found to promote maturation of several components of surfactant. A 2003 review by Howlett and Ohlsson (38) includes three randomized, controlled trials of the use of inositol in preterm infants who had RDS. A significant reduction in death or BPD, stage 4 retinopathy of prematurity, and grade 3 or 4 IVH was seen in the inositol-treated group. No significant increase in adverse effects was reported. Due to the relatively small number of infants in these reviewed trials, multicenter randomized, controlled trials are recommended. However, these early results on the use of inositol in preterm infants with RDS are promising.

**POSTNATAL THYROID HORMONE.** Animal research has shown that antenatal administration of thyroid hormone stimulates surfactant production and reduces the incidence and severity of RDS. A review by Osborn and Hunt (39) examined trials that used postnatal thyroid hormone in preterm infants who had RDS. The conclusion was that administration of thyroid hormone therapy within the first hours after birth had no significant effect on the severity of RDS, morbidity, or mortality in such preterm infants and, therefore, is not recommended.

## Complications and Treatment of RDS

A major pulmonary complication of RDS is the development of BPD, which is generally defined as the need for

oxygen supplementation at 36 weeks' corrected gestational age. (11) Importantly, BPD is not caused by RDS; rather, it can be the result of the many treatments of RDS. (40) The "new BPD," a term coined by Jobe in 1999, describes a syndrome that results from processes that interfere with lung development, not a syndrome resulting only from injury. (40) These processes can include chorioamnionitis, oxygen administration, high tidal volumes, mechanical ventilation, postnatal sepsis, and postnatal corticosteroids. Accordingly, it is possible to develop BPD without having RDS, but BPD absolutely can occur in preterm infants who developed and were treated for RDS. (40) Other complications of RDS in the preterm infant include IVH, patent ductus arteriosus, sepsis, and pulmonary hemorrhage, which likely result from a combination of prematurity, RDS, and its treatments.

Complications from the treatments for RDS are inevitable, but based on risk-to-benefit ratios of the treatments, the complications are mostly tolerable. Antenatal steroids do not have true short-term complications when examined in meta-analyses; there has been no associated increase in maternal death, maternal infection, fetal death, neonatal CLD, or neonatal birthweight. (1) Concerns of decreased birthweight (15) as well as trends toward increased incidence of IVH and long-term adverse behaviors have been voiced with the use of multiple repeat doses of antenatal steroids, but never consistently proven. (16) Interestingly, in a 30-year follow-up of infants who received antenatal corticosteroids, no change in adult size or blood lipid or cortisol concentrations was documented, but there was a slight increase in the incidence of insulin resistance. (13) These results may have implications for the hypothesis of the fetal origins of adult disease. (1)

Mild complications of surfactant administration may include transient oxygen desaturation, apnea, and bradycardia, but such complications typically improve rapidly. (5) More serious complications include endotracheal tube blockage and pulmonary hemorrhage. (5) After administration, surfactant may distribute unevenly to only one lung or certain lobes. A second dose generally follows the same course as the first, which can lead to continued atelectasis of certain areas of the lungs. (9) As mentioned, natural surfactant administration causes an increase in grade 1 and 2 IVH compared with synthetic surfactant. (20) Finally, after surfactant administration, the clinical signs of a PDA may develop earlier in the clinical course. (17)

Complications of mechanical ventilation are not specific to infants being treated for RDS. Air leak syn-

dromes, including PIE and pneumothorax, are more common when the poorly compliant lungs in RDS are mechanically ventilated. (2) Pneumothorax is also associated with the use of nCPAP. (29)

## Long-term Prognosis

Survival of infants who have RDS has improved greatly with the use of antenatal steroids and SRT. Preliminary data in infants treated with antenatal steroids suggest the possibility of less neurodevelopmental delay. (1) Overall, however, information regarding neurodevelopmental outcomes in the preterm infants treated for RDS is lacking, and long-term follow-up studies are needed.

### American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the pathophysiology and risk factors for RDS.
- Recognize the clinical, imaging, and laboratory features of RDS.
- Recognize the pathologic features of RDS.
- Know the clinical strategies and therapies used to decrease the risk and severity of RDS.
- Know the management of RDS, including surfactant replacement.



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## NeoReviews Quiz

10. Normal lung development during fetal life occurs through a series of sequential phases that leads to a mature lung with a large surface area and a minimal diffusion distance for gas exchange. Of the following, the presence of respiratory bronchioles, alveolar ducts, and primitive alveoli in the developing lung is *most* characteristic of the:
  - A. Alveolar phase.
  - B. Canalicular phase.
  - C. Embryonic phase.
  - D. Pseudoglandular phase.
  - E. Saccular phase.
11. In addition to phospholipids, pulmonary surfactant contains four major proteins: surfactant protein (SP)-A, SP-B, SP-C, and SP-D. Each surfactant protein has a specific function. Of the following, SP-B is *most* important for:
  - A. Facilitating formation of tubular myelin.
  - B. Participating in host innate immune defense.
  - C. Promoting adsorption and spreading of surfactant.
  - D. Regulating surfactant reuptake and recycling.
  - E. Regulating surfactant secretion and uptake.
12. Surfactant replacement therapy has been approved by the United States Food and Drug Administration for the treatment of respiratory distress syndrome (RDS) since 1990. Several other therapeutic approaches have been studied as possible adjunct treatments for RDS, as reviewed in meta-analyses published in the *Cochrane Database of Systematic Reviews*. Of the following, the *most* promising adjunct treatment for RDS in preterm infants is the administration of:
  - A. Antithrombin.
  - B. Digoxin.
  - C. Furosemide.
  - D. Inositol.
  - E. Thyroxin.

# ANTENATAL CORTICOSTEROID THERAPY FOR FETAL MATURATION

*This Committee Opinion has been approved by the Executive Committee of the Society of Obstetricians and Gynaecologists of Canada and replaces Committee Opinion No. 53 dated December 1995.*

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## Abstract

**Objectives:** To assess the benefits and risks of antenatal corticosteroid therapy for fetal maturation.

**Options:** To administer antenatal corticosteroids or not to women at risk of preterm birth.

**Outcomes:** Perinatal morbidity, including: respiratory distress syndrome, intraventricular hemorrhage, infection, adrenal suppression, somatic and brain growth; perinatal mortality; and maternal morbidity, including infection and adrenal suppression.

**Evidence:** MEDLINE and PubMed searches 1996 to August 2002 for English-language articles related to antenatal corticosteroid therapy for fetal maturation, the Cochrane Library, and national statements including that of the National Institutes of Health (NIH), the American College of Obstetricians and Gynecologists, and the Royal College of Obstetricians and Gynaecologists.

**Values:** The evidence obtained was reviewed and evaluated by the Maternal-Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and recommendations were made according to guidelines developed by the Canadian Task Force on the Periodic Health Exam.

**Benefits and Harms:** A single course of corticosteroids reduces perinatal mortality, respiratory distress syndrome, and

intraventricular hemorrhage. Information regarding repeat courses of corticosteroids is limited and conflicting, with many studies being retrospective and non-randomized. Some studies suggested a reduction in respiratory distress syndrome with repeat courses, but some found increased rates of neonatal and maternal infection; fetal, neonatal, and maternal adrenal suppression; decreased fetal or neonatal somatic and brain growth; and increased perinatal mortality.

**Recommendations:** The SOGC supports the recommendations of the NIH Consensus Development Panel:

1. All pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course of corticosteroids. (I-A)
2. Treatment should consist of two 12 mg doses of betamethasone given IM 24 hours apart, or four 6 mg doses of dexamethasone given IM 12 hours apart (I-A). There is no proof of efficacy for any other regimen.
3. Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely (II-2E) but be reserved for women participating in randomized controlled trials.

**Validation:** This Committee Opinion has been reviewed and approved by the Maternal-Fetal Medicine Committee of the SOGC and approved by SOGC Council.

## Key Words

Corticosteroid, preterm birth, respiratory distress syndrome, perinatal morbidity and mortality

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## INTRODUCTION

Preterm birth is a significant cause of perinatal morbidity and mortality,<sup>1</sup> accounting for up to 85% of neonatal mortality not caused by lethal malformations.<sup>2</sup> It is a major determinant of serious neonatal and infant morbidity including respiratory distress syndrome (RDS), necrotizing enterocolitis, intraventricular hemorrhage (IVH), and long-term neurodevelopmental handicap.<sup>3</sup>

In addition to its medical importance, preterm delivery has an important economic effect on both short- and long-term care of these preterm infants.<sup>4</sup> The lifetime cost of a surviving preterm infant weighing less than 2500 g, including initial hospitalization, rehospitalization in the first years of life, and long-term morbidity with and without institutionalization, is over \$600,000, with an annual cost in Canada of over eight billion dollars attributed to prematurity.<sup>5</sup>

Despite improvements in perinatal care, the preterm birth rate in Canada has increased from 6.3% in 1981 to 6.8% in 1992 through 1994, a relative increase of 9%.<sup>6</sup>

The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table).<sup>7</sup>

## EVIDENCE AND OPINION

A meta-analysis of studies evaluating the use of corticosteroids in women at increased risk of preterm birth has concluded that a single course of corticosteroids reduced perinatal mortality

(OR 0.60, 95% CI 0.48–0.75), respiratory distress syndrome (OR 0.53, 95% CI 0.44–0.63), and intraventricular hemorrhage (OR 0.48, 95% CI 0.32–0.72).<sup>8</sup> In 1994, the National Institutes of Health (NIH) sponsored a Consensus Development Conference on the effect of corticosteroids for fetal lung maturation on perinatal outcomes, concluding that a single course of corticosteroids should be considered for women at risk of preterm delivery.<sup>9</sup> It concluded that the optimal benefit of corticosteroids lasted for 7 days, and further research was needed to determine the possible benefit of repeat corticosteroid doses 7 days after the initial course.<sup>9</sup> Despite this call for further research, repeat and “rescue” courses of corticosteroids have been increasingly used in clinical practice outside of clinical trials.<sup>9-14</sup>

The NIH again convened a consensus panel in 2000 to address the issue of antenatal corticosteroid use for preterm women, reaffirming the benefit of a single course of corticosteroids, but concluding that current data did not support the routine use of repeat courses.<sup>14</sup>

Previous studies in animal models have tried to evaluate the benefits and risks of repeat courses of corticosteroids. The findings include improved lung mechanics, gas exchange, and maturation,<sup>15-17</sup> but also increased risk of reduced lung, brain, and overall body growth,<sup>14-30</sup> delayed cerebral myelination,<sup>20</sup> as well as deleterious effects on the hypothalamic-pituitary-adrenal axis.<sup>17,21,26,27,30</sup>

Studies in humans of repeat corticosteroids use are limited, many being non-randomized and retrospective, and therefore subject to methodologic problems.<sup>15,30</sup> Some studies suggested a reduction in the incidence and severity of RDS,<sup>30-34</sup> increased

QUALITY OF EVIDENCE ASSESSMENT	CLASSIFICATION OF RECOMMENDATIONS
<p>The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.<sup>7</sup></p> <p>I: Evidence obtained from at least one properly randomized controlled trial.</p> <p>II-1: Evidence from well-designed controlled trials without randomization.</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</p> <p>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations included in this document have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.<sup>7</sup></p> <p>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</p> <p>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</p> <p>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</p>

rates of maternal and neonatal infection,<sup>30,31,35,37</sup> maternal and fetal adrenal suppression,<sup>38-40</sup> decreased fetal or neonatal somatic and brain growth,<sup>31,38,41</sup> and increased perinatal mortality.<sup>36,38</sup>

A randomized trial of single versus weekly courses of antenatal corticosteroids for women at risk of preterm delivery was stopped after an interim analysis found that weekly courses did not reduce composite neonatal morbidity (RR 0.80, 95% CI 0.59–1.10), but resulted in a trend toward more cases of severe IVH (9 vs 2 cases,  $p = 0.06$ ) and chorioamnionitis (24.1% vs 17.8%,  $p = 0.09$ ) in the weekly group.<sup>42</sup> This study has been criticized for being terminated before its calculated sample size could have adequate power to find possible reduction in adverse perinatal outcome.<sup>43,44</sup>

Both betamethasone and dexamethasone have been shown to have benefit for the fetus.<sup>8,14</sup> A recent retrospective study comparing betamethasone and dexamethasone found that betamethasone, but not dexamethasone, reduced the risk of periventricular leukomalacia.<sup>45</sup> This finding has not been reported by other investigators. The NIH consensus panel did not feel that there was enough evidence to recommend betamethasone over dexamethasone.<sup>14</sup> Betamethasone use has been associated with transient reduction in fetal heart rate variability and fetal movement.<sup>46,47</sup>

## RECOMMENDATIONS

The SOGC Maternal-Fetal Medicine Committee, consistent with recommendations of the American College of Obstetricians and Gynecologists<sup>48</sup> and the Royal College of Obstetricians and Gynaecologists,<sup>49</sup> supports the recommendations of the NIH Consensus Development panel:<sup>14</sup>

1. All pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course of corticosteroids. (I-A)
2. Treatment should consist of two 12 mg doses of betamethasone given IM 24 hours apart, or four 6 mg doses of dexamethasone given IM 12 hours apart (I-A). There is no proof of efficacy for any other regimen.
3. Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely (II-2E) but be reserved for women participating in randomized controlled trials.

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