Management of Respiratory Distress Syndrome: An Update

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Introduction
Composition and Metabolism of Surfactant
Surfactant Replacement for Respiratory Distress Syndrome
Ventilatory Management
Nitric Oxide for Premature Babies with Respiratory Distress Syndrome
Summary

Respiratory distress syndrome is the most common respiratory disorder in preterm infants. Over the last decade, because of improvements in neonatal care and increased use of antenatal steroids and surfactant replacement therapy, mortality from respiratory distress syndrome has dropped substantially. However, respiratory morbidity, primarily bronchopulmonary dysplasia, remains unacceptably high. The management of respiratory distress syndrome in preterm infants is based on various modalities of respiratory support and the application of fundamental principles of neonatal care. To obtain best results, a multidisciplinary approach is crucial. This review discusses surfactant replacement therapy and some of the current strategies in ventilatory management of preterm infants with respiratory distress syndrome. Key words: pediatric, respiratory, pulmonary, respiratory distress syndrome, RDS, surfactant replacement therapy, preterm newborn, bronchopulmonary dysplasia. [Respir Care 2003;48(3):279–286. © 2003 Daedalus Enterprises]

Introduction
Respiratory distress syndrome (RDS) is the most common respiratory disorder of premature infants. Since the initial description of the association of RDS with surfactant deficiency more than 30 years ago, enormous strides have been made in understanding the pathophysiology and treatment of this disorder.1 The introduction of antenatal steroids for acceleration of lung maturity and the development of exogenous surfactant can be credited with the dramatic improvement in the outcome of patients affected with RDS.2–6

Typically, RDS affects preterm infants below 35 weeks of gestational age; however, older infants with delayed lung maturation of different etiologies can also be afflicted. Common risk factors associated with RDS include low gestational age, perinatal asphyxia, and maternal diabetes.7 Hack et al have reported that 56% of infants between 501 and 1,500 g were noted to have RDS and/or respiratory insufficiency of prematurity, including 86% between 501 and 750 g; 79% between 751 and 1,000 g; 48% between 1,001 and 1,250 g; and 27% between 1,251 and 1,500 g.8

RDS presents at birth, or shortly thereafter, with grunting respiration, chest wall retractions, nasal flaring, and increased work of breathing. These patients usually show progression of symptoms and require supplemental oxygen. Hypoxemia and hypercarbia, accompanied by various degrees of respiratory and metabolic acidosis, are the typical findings from arterial blood gas analysis. The pathognomonic radiology findings are bilateral, homogeneous, ground-glass appearance of the lung fields, with hypoin-
flation and superimposed air bronchogram. In more severely affected babies, a complete “white-out” of the lung fields is often observed.

The pathophysiology of this disorder has been clearly elucidated. Briefly, the structurally immature and surfactant-deficient lung has a tendency to collapse. The presence of relatively well perfused but poorly ventilated areas of the lung results in ventilation/perfusion mismatch, with hypoxemia and hypercarbia. In some patients, pulmonary vasoconstriction leads to persistence of pulmonary hypertension and right-to-left shunts (via the patent ductus arteriosus and/or the foramen ovale), resulting in more severe hypoxemia. This phenomenon, once thought to be patrimony of the full term infant, is frequently observed in preterm babies with RDS and has led some clinicians to consider the use of inhaled nitric oxide in preterm infants when hypoxemia is unresponsive to adequate support with mechanical ventilation. Fortunately, the natural course of the disease in many low-birthweight infants has been altered by the introduction of exogenous surfactant.

The management of these infants is complex and requires a multidisciplinary team approach to obtain best outcomes. The application of the basic principles of neonatal care, such as thermoregulation, cardiovascular and nutritional support, treatment of early neonatal infection, and prevention of nosocomial infection, is crucial to achieve the therapeutic goals. Clearly, surfactant replacement therapy, continuous positive airway pressure (CPAP), and mechanical ventilation in its different modalities are the mainstay for the respiratory support of these patients.

**Composition and Metabolism of Surfactant**

In the early 1950s, Clements, Pattle, and others described the presence of a thin layer of material on the alveolar surface of the lungs, which is capable of reducing surface tension to a low level upon dynamic compression.9,10 These were the initial descriptions of the physiologic properties and the role of endogenous pulmonary surfactant in the maintenance of alveolar stability. Surfactant is a complex mixture of phospholipids and proteins and is present in the lungs of all mammalian species. Surfactant obtained from alveolar wash contains 80% phospholipids, (phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, and phosphatidylethanolamine), 10% protein (surfactant protein [SP] SP-A, SP-B, SP-C, SP-D and other proteins), and 10% neutral lipids, mainly cholesterol. Phosphatidylcholine, represents 60% of surfactant by weight and accounts for 80% of the phospholipids. Furthermore, saturated phosphatidylcholine is the principal surface-active material in surfactant.11,12

The synthesis of endogenous surfactant is carried out by type II pneumonocytes. The synthetic pathways and enzymes involved in the synthesis of each phospholipid have been characterized. The process takes place in the intracellular organelles of the type II cell and results in the formation of the surfactant lipoprotein complex. Surfactant is subsequently stored in lamellar bodies, which are the intracellular storage granules.

The release of surfactant into the alveolar space, by exocytosis, can be enhanced by several mechanisms, including lung expansion and β receptor stimulation. Once in the alveolar space, lamellar bodies unravel to adopt a lattice-like appearance referred to as tubular myelin. The presence of SP-A and SP-B is essential for the formation of this structure.13 This and other loose arrays of surfactant lipoproteins are thought to constitute the reserve pool from which the surfactant layer that lines the alveoli and small airways is generated and maintained.12 Surfactant leaves the alveolar space and reenters the type II pneumonocytes in the form of small vesicles, which contain small amounts of SP-A and SP-B. In the intracellular space, the surfactant components are recycled.12,13

Pulmonary surfactant contains 3 surfactant-specific proteins: SP-A, SP-B, and SP-C. In recent years, another lung-specific protein, SP-D, has been identified.12 Although not strictly associated with surfactant phospholipids in the alveolar space, SP-D shares certain structural, biochemical, and functional characteristics with SP-A.14 These proteins are synthesized primarily by type II cells, although the presence of messenger ribonucleic acid (mRNA) for their synthesis has been identified in other airway cell types. Though it has been known for several decades that surfactant deficiency can result in RDS in the premature infant, it is only recently that the absence of surfactant proteins has been implicated in the etiology of RDS and other respiratory disorders.15–20

The lack of surfactant proteins precludes tubular myelin formation, a surfactant conformation with surface tension activity, thus promoting alveolar instability and collapse. Low levels of SP-A and SP-B are characteristically found in tracheal secretions and lungs of newborns with RDS.16 Furthermore, an association between the level of SP-A and severity of RDS has been noted.21 Interestingly, in vivo studies with knock-out mice have shown that SP-A is not crucial for surface-tension-lowering activity or surfactant homeostasis. This is consistent with the fact that the available surfactants, which have well-documented efficacy, do not contain surfactant protein A. However, SP-A-deficient animals are more prone to infections, highlighting the importance of SP-A in host defense against pathogens.

SP-B, present in the available surfactants in various concentrations, is critical for surface-tension-lowering activity at birth, formation of lamellar bodies, and surfactant homeostasis. SP-B deficiency is associated with a severe form of RDS unresponsive to surfactant replacement. These patients generally die despite intensive care. Lung trans-
plantation has been used in a handful of patients and is currently the only therapeutic option.

Recently, an association of SP-C gene mutation and familial interstitial lung disease has been reported. It is unclear whether SP-C-based surfactant replacement will be efficacious for these patients. The role of surfactant proteins during the acute and the recovery phase of various respiratory disorders in the newborn period is still under intensive investigation.

**Surfactant Replacement for Respiratory Distress Syndrome**

Over the last 2 decades, our understanding of the use of surfactant for the treatment of RDS has increased substantially. The administration of exogenous surfactant for the treatment of RDS in preterm infants is probably the most thoroughly evaluated therapy currently used in neonatal intensive care units. Avery and Mead’s seminal report on the role of surfactant deficiency in the pathophysiology of RDS, then referred to as hyaline membrane disease, brought the facts from bench to bedside. Since then, great strides have been made in understanding the pulmonary surfactant system. Fujiwara et al, in Japan, pioneered the introduction of surfactant replacement for the treatment of RDS. In a small, uncontrolled trial, 10 mechanically ventilated infants with clinical and radiologic diagnoses of severe RDS were successfully treated with a modified bovine surfactant extract (Surfactant-TA, Surfacten, Tokyo Tanabe, Tokyo, Japan) administered via endotracheal tube. All infants demonstrated remarkable improvement in oxygenation and decreased ventilatory requirements. Numerous multicenter, randomized, controlled studies have since evaluated and confirmed the efficacy and safety of various surfactant preparations, both natural and synthetic, since evaluated and confirmed the efficacy and safety of numerous multicenter, randomized, controlled studies have demonstrated that repeated dosing is more effective in reducing mortality rate than single-dose therapy. Multiple-dosing may help oxygenation by overcoming surfactant inactivation, and by reaching previously atelectatic areas of the lungs re-expanded after the initial dose of surfactant.

Two therapeutic approaches have been evaluated: prophylactic and rescue treatments. Prophylactic administration of surfactant, given within minutes after birth, offers the theoretical advantage of replacing surfactant before severe RDS develops. Animal data suggest that ventilation of the surfactant-deficient lung with high volumes, even for a few breaths, may decrease the subsequent response to surfactant replacement. Additionally, a more homogeneous distribution of surfactant may be obtained when administered to the partially fluid-filled lungs, immediately after birth. Prophylactic administration of surfactant could theoretically decrease the adverse effects of barotrauma and volutrauma in the noncompliant lung, and thus reduce the incidence of bronchopulmonary dysplasia (BPD). In clinical trials, early therapy did seem to reduce the need for subsequent readministration and the requirement for supplemental oxygen and mechanical ventilation.

On the other hand, prophylactic therapy is more likely to be associated with administration errors related to suboptimal endotracheal tube placement. Furthermore, this approach could result in many babies being unnecessarily treated, depending on the gestational age below which prophylactic surfactant is being considered.

Rescue treatment is indicated for patients with established RDS who require mechanical ventilation and supplemental oxygen. The major advantage of this approach is that surfactant would be administered only to those patients with clinical and radiographic diagnosis of RDS. The delivery of surfactant would take place in a more controlled situation in the intensive care unit, once the patient is stabilized. Therefore, rescue therapy may decrease cost and morbidity associated with unnecessary surfactant treatment. The down side of this approach is that the delay of surfactant replacement may decrease its efficacy and allow the progression of lung injury. Our approach has been to provide resuscitation and stabilization of the very-low-birthweight infant in the delivery room, and to administer surfactant as early as possible after radiographic confirmation of RDS and assessment of proper endotracheal tube placement. Unfortunately, not every baby
with RDS from surfactant deficiency responds favorably to this treatment. The need for high oxygen concentration, and high ventilatory pressure during the early stages of RDS have been identified as risk factors for an inadequate response. Whether the lack of response to surfactant is secondary to the initial severity of the disease or to the damage induced by short periods of aggressive ventilation prior to or after surfactant replacement is not clear.

In contrast to the remarkable effects of surfactant therapy on RDS, the incidence of other morbidities, including intraventricular hemorrhage (IVH), sepsis, patent ductus arteriosus, and BPD, has not been substantially altered by surfactant therapy. The lack of a more marked effect of surfactant replacement on BPD is not too surprising, since the etiology of BPD is multifactorial and cannot be attributed solely to surfactant deficiency. BPD has been traditionally defined as the need for supplemental oxygen at 28 days of life, with chronic radiologic changes. More recently, the need for supplemental oxygen at 36 weeks corrected postconceptional age has been used as a diagnostic criterion. Although the deleterious effects of barotrauma/volutrauma and oxygen toxicity on the surfactant-deficient lung are paramount in the pathogenesis of BPD, a number of prenatal and postnatal factors have also been implicated (low gestational age, low birthweight, male sex, white ethnicity, patent ductus arteriosus, and prenatal and postnatal infection). Furthermore, many preterm infants develop BPD without antecedent RDS. The developmental immaturity of the protective antioxidant systems, such as superoxide dismutase, catalase, and vitamin E, may make the very-low-birthweight infant particularly susceptible to oxygen toxicity. Although individual studies have shown a decreased incidence of BPD, these results have not been substantiated by meta-analysis of large, randomized trials. When different weight categories are analyzed, in the larger infants (birthweight > 1,250 g) in whom BPD may be more directly associated with surfactant deficiency and the effects of volutrauma/barotrauma, a trend toward a lower incidence of BPD emerges. With more immature infants surviving, a significant increase in BPD might be expected. However, the introduction of surfactant has significantly decreased mortality from RDS, without a substantial increase in BPD rate. Data from clinical trials suggest that more infants are surviving both with and without BPD.

**Ventilatory Management**

The goals of ventilatory management during the early stages of RDS are to maintain adequate oxygenation and ventilation, while minimizing ventilator-induced lung injury. The surfactant-deficient lung of the immature infant characteristically has decreased lung compliance, increased elastic recoil, and reduced functional residual capacity. In infants with RDS, surfactant administration rapidly improves oxygenation by increasing functional residual capacity and reversing atelectasis. The acute changes in lung volume following surfactant administration increase the surface area available for gas exchange. Though oxygenation improves quickly, changes in lung compliance occur more gradually. It is very important to recognize this window of opportunity to appropriately wean inspired oxygen concentration and ventilatory support, to prevent lung injury.

Because of increased survival of more immature infants, ventilator-induced lung injury in the form of BPD has become a major concern for caregivers. Interestingly, a substantial center-to-center variability in the incidence of BPD has been reported. One could argue that, at least to some extent, differences in ventilatory approach might be responsible for the observed variation.

Conventional mechanical ventilation, primarily time-cycled, pressure-limited ventilation, has traditionally been used in neonatal intensive care units for the management of RDS. Over the last 20 years, the technologic advancement of ventilators has provided the practitioner with a variety of new modalities, such as patient-triggered ventilation, pressure-controlled ventilation, and volume-guaranteed ventilation. Several randomized, controlled trials have shown encouraging short-term benefits, such as fewer days on mechanical ventilation and less need for sedation. However, these studies did not have the statistical power to demonstrate a significant decrease in the incidence of BPD.

The introduction of high-frequency ventilation (high-frequency oscillatory ventilation [HFOV], high-frequency jet ventilation, and flow interruption) was received with great enthusiasm by neonatologists and therapists. These techniques were loaded with great promise but, unfortunately, several randomized trials have provided us with mixed results in regard to pulmonary outcomes. Furthermore, serious concerns have been raised regarding the safety of these modalities for use in premature babies. Wiswell et al reported more IVH and periventricular leukomalacia with high-frequency jet ventilation than with conventional ventilation, and speculated that hypocarbia might play a role. A Cochrane systematic review on the subject reinforced these concerns. This was in contrast with a meta-analysis by Clark et al of 9 studies that showed no such an association. Two recently published large, randomized, controlled trials, one from the United Kingdom Oscillation Study Group (the UKOS trial) and one from Courtney et al in the United States, showed no difference in adverse neurological outcomes (IVH or periventricular leukomalacia); however, results on the primary outcome, BPD, were discordant. The United States trial compared HFOV with synchronized intermittent
mandatory ventilation and demonstrated a modest benefit in pulmonary outcomes. Babies allocated to the HFOV group were extubated at an earlier age (13 vs 21 d), and there was a small but significant increase in survival without supplemental oxygen at 36 weeks corrected age. The United Kingdom trial, in which 3 different high-frequency oscillation ventilators were used, showed no significant differences in the incidence of BPD, death, or other complications. It is important to recognize the substantial center-to-center variability of experience with this ventilation modality, which probably accounts for the differences in reported outcomes. Furthermore, the question of whether high-frequency ventilation should be used as a primary mode of ventilation or a rescue modality remains unresolved, mainly because of serious concerns regarding central nervous system complications.

In recent years, permissive hypercapnia, a strategy intended to minimize ventilator-induced lung injury, has gained popularity. Briefly, in this approach, the patient’s arterial carbon dioxide concentration is kept between 45 and 55 mm Hg. In animal models the use of permissive hypercapnia was associated with less lung injury. Furthermore, clinical studies in adults with acute respiratory distress syndrome have shown increased survival. Theoretically, the potential advantages from this approach include less volutrauma, fewer adverse effects from hypocapnia, and increased oxygen unloading. Whether this may translate into a decrease in the incidence of BPD is unclear. Also, the potential disadvantages from sustained high carbon dioxide levels in premature infants, including hypoxemia, cerebral vasodilation, increase in IVH, and retinopathy of prematurity, cannot be ignored. Clearly, careful evaluation of this approach is necessary. In a large, multicenter, randomized, controlled trial, which included 220 patients with birthweights between 501 and 1,000 g, permissive hypercapnia was not associated with a reduction of BPD. Interestingly, in the hypercapnia group there was significantly less need for ventilatory support at 36 weeks corrected age (1% vs 16% in the control group), whereas there were no differences in other morbidities. Unfortunately, this study was terminated prematurely because of substantial complications (eg, spontaneous intestinal perforation) arising from the concurrent use of steroids.

All forms of mechanical ventilation of the immature lung probably promote some degree of ventilator-induced lung injury. Therefore, techniques that favor spontaneous breathing with early lung recruitment may be required to decrease BPD. Early lung recruitment is crucial and imperative to reduce the deleterious effect of atelectrauma and should probably begin in the delivery room.

In recent years, there has been a renewed interest in noninvasive modalities of respiratory support, specifically, CPAP. The use of CPAP, originally introduced in the early 1970s by Gregory for the treatment of infants with RDS, has steadily increased since the early 1990s and regained an important place in the management of RDS. There are clear benefits of CPAP over mechanical ventilation of the immature lung. Animal studies with premature lambs showed that CPAP decreases the influx of granulocytes and the presence of hydrogen peroxide formation (a marker of white cell activation) in alveolar lavage cells, compared to mechanically ventilated animals. In a randomized, controlled trial by the National Institute of Child Health and Human Development Neonatal Research Network, the use of surfactant and early extubation to CPAP in babies between 1,250 and 2,000 g showed a decreased need for and duration of mechanical ventilation. Unfortunately, the trial was halted early because of lack of enrollment. A similar multicenter, randomized trial by Verder et al showed similar results. None of these studies showed a reduction in oxygen dependence at 28 days or 36 weeks corrected gestational age. From current available evidence, one could conclude that nasal CPAP after surfactant replacement is a reasonable alternative treatment for premature infants with RDS; however, the effect on the incidence of BPD is less clear. Whether the addition of synchronized intermittent mandatory ventilation to nasal CPAP will reduce the need for reintubation in some of the smaller patients, who frequently develop apnea, is not clear. Increasing gestational age and prophylactic surfactant are important variables associated with a higher success rate.

The development of new ventilatory modalities may be required to decrease ventilator-induced lung injury and to maximize the beneficial effects of surfactant therapy. The challenge to improve long-term pulmonary outcomes in the high-risk population has not yet been met.

**Nitric Oxide for Premature Babies with Respiratory Distress Syndrome**

Several randomized, controlled trials performed during the last decade provide solid scientific evidence about safety, patient selection criteria, dosage, and short-term and long-term outcomes associated with inhaled nitric oxide in term and near-term babies. Therefore, in 1999 inhaled nitric oxide received United States Food and Drug Administration approval and is now widely used for the treatment of infants with hypoxic respiratory failure, primarily persistent pulmonary hypertension of the newborn. Some preterm infants with severe RDS, who develop persistent hypoxemia due to pulmonary vasoconstriction, could potentially benefit from this therapy. Several small trials have now evaluated acute responses to inhaled nitric oxide in preterm infants and demonstrated significant improvement in oxygenation, but no differences in mortality. However, little is known about the potential adverse effects of inhaled nitric oxide in this population of patients.
in whom complications could be more severe, such as increase in IVH. Several randomized, controlled trials are currently underway, which, it is hoped, will address some of the important currently unresolved issues. The potential benefits of inhaled nitric oxide for the prevention of chronic lung disease is another area of intense research. The currently available evidence is insufficient to recommend the use of inhaled nitric oxide outside randomized, controlled trials in this population, although we have used it in exceptional circumstances, under a compassionate care protocol, with parental informed consent.

Summary

Despite the tremendous advances in the management of RDS, substantial respiratory morbidity in the form of BPD remains a major problem. Prenatal corticosteroids for lung maturation and postnatal surfactant replacement therapy significantly reduce the incidence, severity, and mortality associated with RDS and are currently considered standard of care. Only natural surfactants are currently available for use in the United States, and there are no significant differences in clinically important outcomes among preparations.

The ventilatory management of babies suffering RDS may require further refinement. The new generation of ventilators may allow us to better monitor and control tidal volume delivery to minimize volutrauma while preventing unwanted atelectasis. Based on the currently available clinical data, there is no significant difference in outcomes between conventional and high-frequency ventilation for the management of RDS, although there is considerable center-to-center variation in outcomes. Recent data suggest that HFOV, when used properly, does not seem to increase the incidence of intracranial hemorrhage. Nasal CPAP may reduce the damaging effects of mechanical ventilation on the developing lung. Finally, the general principles of neonatal care and a team approach should be applied to maximize the occurrence of good short-term and long-term outcomes.

REFERENCES


Hansell: At the American Association for Respiratory Care Open Forum last year, Jeanette Asselin’s group presented some preliminary data on the use of early HFOV, and I believe those data were very encouraging for early use of HFOV.

**Discussion**

Wiswell: I was on the steering committee for the study you refer to. It’s one of the few HFOV trials that have shown benefits. They found less mortality and BPD at 36 weeks’ post-conception age with HFOV than with conventional ventilation. The study is going to be published in the New England Journal of Medicine. In that same issue of that journal will appear what’s known as the “UKOS” trial, from the United Kingdom Oscillation Study Group, which found no differences in outcomes. The problem with the latter trial, from my perspective, is that too many centers were involved and too many different types of devices were used. Three different kinds of high-frequency oscillator were involved, so I think they were comparing apples to oranges.

**REFERENCES**

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Rodriguez: I appreciate that comment. That reinforces the fact that for each report describing beneficial effects from HFOV, you can find another one that shows no benefits or shows potential complications with HFOV. My personal bias is that there is very substantial center-to-center variability. If I’m born in Provo, Utah, I’d probably like to be on HFOV. But if I’m born somewhere else, maybe not. Maybe clinicians just use what they are used to and feel more comfortable with.

I think HFOV has a role in the management of babies with RDS. At our center we use it as a rescue modality, and maybe that’s a little late, since the lungs have already suffered all the damage, and probably that’s why we don’t see significant benefits. I think there is a subset of patients who may benefit from early institution of HFOV and may never need a conventional ventilator. The Cochrane systematic review cannot reconcile that HFOV is better than conventional ventilation.

There are some concerns, and Tom Wiswell published a very interesting article in 1996, although he used a different strategy, which was termed the “low volume” strategy at that time, and he raised a very interesting question that has also been raised by other investigators, and that’s central nervous system morbidities— ischamic lesions in the form of periventricular leukomalacia and increased incidence of IVH. Some of the newer trials, in which an optimal lung volume strategy was used, did not find differences in those outcomes. There seemed to be no difference in the incidence of IVH. However, I’m still a little reluc
tant to suggest that everybody should put kids on HFOV right off the bat.

REFERENCES

Donn: Regarding the study by Courtney et al, I think we should be careful not to over-interpret the results. It only compared HFOV to synchronized intermittent mandatory ventilation, and that might not be the best mode to begin a newborn who has RDS.

REFERENCE

Rodriguez: Absolutely.

Myers: John Salyer and his colleagues recently published a report in Respiratory Care on the use of aerosolized β agonists, inhaled corticosteroids, in the RDS population. The question is, what’s the efficacy of β agonists, or how do you determine efficacy in a very small baby, in whom it is difficult to measure lung compliance and resistance?

REFERENCE

Rodriguez: That’s a very good point. Actually, I’m a little concerned about the early use of β agonists in babies with RDS. I’m not sure whether there is a role for β agonists early on in the course of RDS. β stimulation facilitates lung fluid re-absorption, and some of these babies may have some retained lung fluid, which from my point of view is good initially, because it facilitates surfactant spread and surfactant distribution when you’re treating them. I like to give surfactant when there is still some lung fluid in place, because the surfactant will be better distributed in the lung.

I don’t know of any data that strongly suggest that the early use of β agonists makes a substantial difference in the management of these babies. Also, there is evidence that suggests that some of the β agonists that we use in the neonatal intensive care unit have an inflammatory effect in the lung, at least when used chronically in asthmatic adults. I’m a little concerned when I see babies who are 3, 4, or 5 days old started on β agonists, because that may be promoting more lung inflammation than we know. Before more data are available I’m a little reluctant to introduce β agonists into the airway of a baby who is in the acute phase of RDS.

REFERENCE