



eNeonatal Review

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COURSE DIRECTORS

Edward E. Lawson, M.D.
Professor
Department of Pediatrics – Neonatology
The Johns Hopkins University School of Medicine

Lawrence M. Noguee, M.D.
Associate Professor
Department of Pediatrics – Neonatology
The Johns Hopkins University School of Medicine

Christoph U. Lehmann, M.D.
Assistant Professor
Department of Pediatrics – Neonatology
The Johns Hopkins University School of Medicine

Lorraine A. Harbold, R.N., M.S.
The Johns Hopkins Hospital;
NICU Education Coordinator

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It is unarguable that the number of patients and the amount of clinical data collected in randomized controlled trials of surfactant preparations over the past 15 years dwarf that of any other clinical arena in neonatology. Many of these trials serve as model templates for the design and execution of future clinical studies. Nonetheless, for all the useful information learned, there are still intriguing questions about surfactant therapy in newborns for which answers are incomplete or controversial.

Reviews & Commentary

Mark L. Hudak, MD

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Guest Editor of the Month

Mark L. Hudak, MD

Assistant Dean
Professor and Assistant Chairman
Department of Pediatrics
University of Florida at Jacksonville



Guest Faculty Disclosure

Mark L. Hudak, MD

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COMMENTARY

Many neonatologists still question whether the strategy of early surfactant prophylaxis after premature birth results in better clinical outcomes than a more conservative "rescue" protocol. Although many NICUs have adopted some prophylaxis protocol for the most extremely premature infants (24-26 weeks' gestation), there is no consensus on this issue for infants of more advanced gestations. The largest and most carefully conducted studies with available commercial surfactants support the notion that prophylaxis improves survival through 30 weeks' gestation.

One argument that has been advanced against routine prophylaxis notes that current use of antenatal steroids is now much more frequent (70%-90%) than at the time of the prophylaxis vs. rescue trials (20-30%). Hence, especially among infants of intermediate prematurity, the incidence of severe RDS can be expected to be much lower, thereby allowing a greater clinical buffer regarding the timing of initial surfactant treatment. Inferences drawn from large databases (weaknesses acknowledged) are that the combination of antenatal steroids and prophylactic surfactant improves overall outcome (not solely respiratory) compared to either antenatal steroids or surfactant therapy alone. This inference has solid underpinnings in the experimental animal literature.

Somewhat similarly, a second argument centers on the interim enhancements to conventional ventilation and the increased availability of high frequency ventilation (HFV). However, there is no controlled evidence that refinements in conventional ventilation have reduced mortality nor is there even consensus that early use of HFV is advantageous compared to conventional ventilation. Accordingly, altering surfactant administration strategies on account of the "benefits" associated with these refinements in mechanical ventilatory techniques seems unwarranted.

One small study does suggest a continued benefit to prophylactic vs. rescue surfactant administration in the setting of high frequency oscillation as the primary mode of ventilation (Plavka R et al: see sources for additional information below.) More recently enthusiasts have advocated the practice of deferring prophylactic surfactant in favor of delivery room application of nasal CPAP. The rationale is that immediate inflation of the lungs after birth with stabilization of a normal functional residual capacity via nasal CPAP accomplishes the therapeutic equivalent of exogenous surfactant administration. Randomized controlled trials of this approach compared with prophylactic surfactant followed by ventilation have not been reported.

Perhaps no issue in this field generates more controversy among neonatologists than the choice of optimal surfactant preparation. The only comparative study of Survanta (beractant) and Infasurf (calfactant) provides little independent basis of an efficacy differential (other than a longer duration of action) for choosing one surfactant over the other. Among infants in the prophylaxis arm with birth weights less than 600 grams, the Survanta group showed a surprisingly lower than expected mortality rate, while the Infasurf group showed mortality as expected in this population. Clear preclinical differences in efficacy did not translate into perceptibly improved clinical outcomes. This underpowered trial is just one of many illustrations of how the significant "noise" introduced by the complex biology of preterm birth and its aftermath muddies comparative therapeutic evaluations. It can only be hoped that a future publication of the results of a large ($n > 2000$) repeat comparison trial of these two surfactants (completed by the Pediatrix network in November 2003) will provide more definitive clinical guidance.

Most centers have expanded indications for surfactant therapy to include term and near-term infants with meconium aspiration syndrome (MAS) and pneumonia who are intubated and require significant ventilatory support. The severity threshold for intervention varies by center and even by individual neonatologist within a center. Since the publication of the studies by Findlay et al and Lotze et al, high frequency oscillatory ventilation and inhaled nitric oxide therapy have become more routine. The question of whether surfactant replacement confers additional advantage in this practice setting may never be perfectly answered. Based on the limited evidence, intervention at a less severe stage of disease and commitment to two or three total doses once treatment is begun both appear to be prudent pathways. Further investigation would be necessary to

determine whether surfactant treatment at an earlier stage in the disease process (e.g., for infants who are on hood oxygen or nCPAP support; or for infants who are ventilated with $OI < 15$) is safe and effective. After an initial positive report, there have been no subsequent follow-up data concerning lung lavage with dilute surfactant. At this point, the benefit to risk profile for this novel intervention remains unknown compared both to control treatment and to standard surfactant replacement therapy.

Finally, the genetic studies remind us that not all surfactant deficiency conditions are related to immaturity or to inactivation of normal surfactant. In infants with atypical respiratory disease, deficiencies of the hydrophobic surfactants (SP-B and SP-C) should be considered. Because SP-B deficiency has been reported to account for less than 20% of a highly selected cohort of babies with respiratory failure not due to obvious disease conditions, there is little doubt that other genetic bases for surfactant dysfunction will continue to be identified.

SOURCES FOR ADDITIONAL INFORMATION

Plavka R et al: Early vs. delayed surfactant administration in extremely premature neonates with respiratory distress syndrome ventilated by high-frequency oscillatory ventilation. Intensive Care Med 2002; 28:1483-1490.

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Moller JC, Schaible T, Roll C, Schiffman JH et al: Treatment with bovine surfactant in severe acute respiratory distress in children: a randomized multicenter study. Intensive Care Med 2003; 29:437-446

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Prophylaxis vs. Rescue Surfactant Treatment for Very Premature Infants

Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, Sinkin RA, Bartoletti A, Dweck HS, Horgan MJ, Risemberg H, Phelps DL, Shapiro DL: A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. N Engl J Med 1991; 324:865-871

Kattwinkel J, Bloom BT, Delmore P, Davis CL, Farrell E, Friss H, Jung AL, King K, Mueller D: Prophylactic administration of calf lung surfactant extract is more effective than early treatment of respiratory distress syndrome in neonates of 29 through 32 weeks' gestation. Pediatrics 1993;92:90-98.

Kendig JW, Ryan RM, Sinkin RA, Maniscalco WM, Notter RH, Guillet R, Cox C, Dweck HS, Horgan MJ, Reubens LJ, Risemberg H, Phelps DL: Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics 1998; 101:1006-1012.

Soll RF: Surfactant therapy: does timing of treatment improve clinical outcome? Neonatal Respiratory Diseases 2002; 12:1-8.

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two questions of treatment breakpoint and of timing of initial prophylaxis.

Kendig et al reported that 479 infants with a gestational age of less than 30 weeks were randomized to receive either a preventilatory dose of surfactant or to receive treatment when they required either 40% inspired oxygen or a mean airway pressure of ≥ 7 cm H₂O. Fifty-eight percent of the infants in the latter group eventually received surfactant. Survival to discharge was significantly higher in the prophylaxis group compared to the rescue group (88% vs 80%), particularly in the subgroup of infants at or below 26 weeks' gestation (75% vs. 54%). Infants who received prophylaxis also had less severe RDS and fewer pneumothoraces; however, this group developed the same incidence of chronic lung disease as those infants randomized to the rescue treatment.

Kattwinkel and colleagues extended these observations in a study that enrolled 1248 infants born between 29 and 32 weeks' gestational age. Infants were randomized to early prophylaxis (not necessarily preventilatory, but treated by 5 minutes of age) or treatment at such time as mild RDS was diagnosed (median age of 1.5 hours). Infants were re-treated when they required a mean airway pressure ≥ 10 cm H₂O and FiO₂ ≥ 0.60 to maintain PaO₂ > 70 mm Hg. Death (0.5% vs. 1.8%) and death or BPD (5% vs. 9%) were significantly lower in the prophylaxis compared to the rescue group. Other respiratory and non-respiratory morbidities did not differ between the two groups.

In the third trial, also led by Kendig, 651 infants born between 24 to 28 weeks' gestation were randomized to two different surfactant prophylaxis strategies: immediate administration once intubated (preventilatory) vs. treatment after stabilization (postventilatory). In the postventilatory group, survival to discharge was slightly higher and the requirement for supplemental oxygen at 36 weeks' corrected gestational age was slightly lower.

Finally, a meta-analysis by Soll that included 5 additional studies with different study designs concluded that surfactant prophylaxis does improve neonatal outcomes. It was noted that by 1998 that the Vermont-Oxford network centers had not uniformly translated the results of these studies into routine clinical protocols.

Kendig JW, Notter RH, Cox C, Reubens LJ, Davis JM, Maniscalco WM, Sinkin RA, Bartoletti A, Dweck HS, Horgan MJ, Risemberg H, Phelps DL, Shapiro DL: A comparison of surfactant as immediate prophylaxis and as rescue therapy in newborns of less than 30 weeks' gestation. N Engl J Med 1991; 324:865-871

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Clinical Comparisons of Commercial Surfactants

Horbar JD, Wright LL, Soll RF et al: A multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. J Pediatr 1993;123:757-766.

Vermont-Oxford Neonatal Network: A multicenter randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory distress syndrome. Pediatrics 1996;97:1-6.

Hudak ML, Farrell EE, Rosenberg AA, et al: A multicenter randomized masked comparison of natural vs. synthetic surfactant for the treatment of respiratory distress syndrome. J Pediatr 1996;28:396-406.

Hudak ML, Martin DJ, Egan EA et al: A multicenter randomized masked comparison trial of synthetic surfactant vs. calf lung surfactant extract in the prevention of neonatal respiratory distress syndrome. Pediatrics 1997;100:39-50.

Bloom BT, Kattwinkel J, Hall RT et al: Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome. Pediatrics 1997;100:31-38.

Animal-based surfactants containing surfactant proteins B and C exhibit significantly greater efficacy in biophysical and animal physiological assays than synthetic surfactants. These preclinical assays have correlated reasonably well with the results of large randomized comparative clinical trials in premature neonates. Each animal-based surfactant preparation has a unique surfactant protein and phospholipid profile that translates into smaller but still substantial differences among these drugs in preclinical efficacy. To date, no study in infants has been adequately powered to determine whether the choice of a particular natural surfactant impacts survival, chronic lung disease, or air leak complications associated with RDS.

Exosurf Neonatal (a synthetic surfactant) and Survanta (a modified bovine-derived surfactant) were the first two FDA-approved surfactant preparations. The initial two publications summarize randomized unmasked trials that compared the efficacy and safety of these surfactants in the treatment of established RDS. Horbar et al, in an NIH-sponsored trial (n=617), found that Survanta treatment resulted in a lower average F_{iO_2} and MAP for 72 hours after treatment.

Survanta treatment was associated with a non-significant reduction in the incidence of death or BPD (62% vs. 67%) and pneumothorax (9% vs. 13%). The larger (n=1500) Vermont-Oxford network study also noted a significant attenuation of respiratory disease associated with Survanta therapy as well as a decreased incidence of air leak. Survival without BPD was higher in the Survanta treatment group, although these numbers did not reach statistical significance. Despite these rather modest findings, these two studies accelerated an ongoing transition from Exosurf to Survanta as the surfactant of choice in NICUs across the country.

Subsequently, Hudak et al conducted a masked randomized study that compared Exosurf and Infasurf (an extract of calf lung lavage) for the treatment of established RDS (n=1033). Infasurf treatment was associated with significant reductions in the severity of RDS, in the incidences of pneumothorax and pulmonary interstitial emphysema, and in the duration of assisted ventilation. The magnitudes of these treatment effects equaled or exceeded those that had been found in the Exosurf-Survanta trials, but no significant effect on longer term outcomes such as survival or BPD was demonstrated. A concomitant study, also led by Hudak, that compared these two surfactants for the prophylaxis of RDS in infants less than 29 weeks' gestation (n=871), observed significant reductions in the incidence and severity of RDS, the incidence of air leak, and in RDS-related mortality -- but no differences in survival to discharge or in the incidence of BPD.

The comparative trial most germane to current clinical practice is the Survanta vs. Infasurf trial conducted by Bloom et al. However, the sample sizes (prophylaxis arm n=374 and rescue arm n=608) were not large enough to provide definitive guidance about the optimal choice of surfactant preparation. The intervals between doses were greater for Infasurf and suggested a longer duration of treatment effect, but mitigation of respiratory support in the acute phase of RDS was defined only in the treatment arm. No differences were seen in short- or long-term outcomes, although mortality was higher in the subgroup of infants with birth weights < 600 grams who received Infasurf prophylaxis (63% vs. 26%, $P < .01$).

Horbar JD, Wright LL, Soll RF et al: A multicenter randomized trial comparing two surfactants for the treatment of neonatal respiratory distress syndrome. J Pediatr 1993;123:757-766.

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Vermont-Oxford Neonatal Network: A multicenter randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory distress syndrome. *Pediatrics* 1996;97:1-6.

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Surfactant Therapy for Non-RDS Respiratory Diseases

Findlay RD, Taeusch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome: *Pediatrics* 1996;97:48-52.

Lotze A, Mitchell BR, Bulas DI, Zola EM, Shalwitz RA, Gunkel JH, and the Survanta In Term Infants Study Group: Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. *J Pediatr* 1998;132:40-7.

Willson DF, Zaritsky A, Bauman LA, Dockery K, James RL, Conrad D, Craft H, Novotny WE, Egan EA, Dalton H: Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. *Crit Care Med* 1999;27:188-95.

Wiswell TE, Knight GR, Finer NN, Donn SM, Desai H, Walsh WF, Sekar KC, Bernstein G, Keszler M, Visser VE, Merritt TA, Mannino FL, Mastroianni L, Marcy B, Revak SD, Tsai H, Cochrane CG: A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. *Pediatrics*. 2002;109:1081-7.

Surfactant therapy was found to improve respiratory function in some parenchymal lung diseases other than RDS. In addition, early intervention as well as a multi-dose regimen appeared to impact efficacy

The groundwork for surfactant replacement for meconium aspiration syndrome is founded in *in vitro* and in animal experiments in which meconium inhibited/inactivated surfactant function; this inhibition was reversed in a dose-dependent manner with exogenous surfactant. Findlay and

colleagues randomized 40 term infants with (MAS) who required ventilatory support to a course of Survanta (up to four doses at 6 hour intervals) or air placebo. Infants had moderate respiratory dysfunction with mean OIs in the low 20s. Survanta-treated infants demonstrated a mild improvement after the initial dose, but exhibited a dramatic decrease in OI following second and third doses. Only one of the 20 Survanta-treated infants vs. 6 of 20 control infants required ECMO support. The durations of mechanical ventilation, oxygen therapy, and hospitalization were significantly lower in the Survanta treated group.

A larger study (n=328) by Lotze et al expanded the use of Survanta to the treatment of infants with sepsis/pneumonia and PPHN in addition to meconium aspiration syndrome. Infants were randomized by disease and by OI strata to treatment with surfactant or air-placebo. The need for ECMO was designated as the primary outcome variable. Survanta treatment did not change mortality but was associated with a 27% reduction (from 40.4% to 29.7%) in the need for ECMO. This treatment effect was greatest (40%) in infants with sepsis, intermediate (27%) in infants with meconium aspiration syndrome (MAS), and not significant (7%) in infants with PPHN. Also of note was the observation that a significant improvement in the primary outcome was seen only among infants who at the time of study entry had the least severe disease (OIs 15-22). Contrary to the Findlay study, no differences in durations of ventilation or hospitalization were noted.

Our critical care colleagues, headed by Willson, have reported one small (n=42) randomized unmasked trial of Infasurf for the treatment of children with acute hypoxemic respiratory failure characterized by need for ventilatory support, an OI > 7, and radiographic findings of diffuse bilateral pulmonary infiltrates. Children treated with Infasurf demonstrated more rapid improvement in respiratory function and were extubated 4 days sooner and hospitalized 5 days less compared to control patients. (See also Moller JC, et al in SOURCES FOR ADDITIONAL INFORMATION)

More recently, Wiswell et al reported a unique randomized trial in term and near-term infants with MAS treated with Surfaxin, a synthetic surfactant composed of phospholipids and a synthetic peptide designed as an analog surfactant protein B. The treatment intervention consisted of three serial bronchoalveolar lung lavages, each employing 8 mL/kg of dilute Surfaxin. Surfaxin lavage reduced OI for 96 hours after treatment and resulted in a non-significant reduction in duration of ventilation. No side effects of treatment were noted in this initial study.

Findlay RD, Taeusch HW, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome: Pediatrics 1996;97:48-52.

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Lotze A, Mitchell BR, Bulas DI, Zola EM, Shalwitz RA, Gunkel JH, and the Survanta In Term Infants Study Group: Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. J Pediatr 1998;132:40-7.

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Clinical Expression of Defects in Surfactant Proteins B and C

Nogee LM, deMello DE, Dehner LP, Colten HR: Brief report: deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med* 1993;328:406-410.

Nogee LM, Dunbar AE, III, Wert SE, Askin F, Hamvas A, Whitsett JA: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med* 2001;344:573-579.

Tredano M, Griese M, de Blic J, et al. Analysis of 40 sporadic or familial neonatal and pediatric cases with severe unexplained respiratory distress: relationship to SFTPB *Am J Med Genet* 2003; 119A:324-39.

Thomas AQ, Lane K, Phillips J, et al. Heterozygosity for a Surfactant Protein C Gene Mutation Associated with Usual Interstitial Pneumonitis or Cellular Nonspecific Interstitial Pneumonitis in One Kindred. *Am J Respir Crit Care Med* 2002; 165:1322-1328.

Animal derived exogenous surfactant preparations contain the hydrophobic surfactant proteins SP-B and SP-C. Surfactant replacement experiments in animal models and evidence from genetically engineered mice models have demonstrated the importance of these proteins in surfactant function. Different mutations of the SP-B and SP-C genes are now recognized to cause a varied phenotype of respiratory disease ranging from lethality in the neonatal period to chronic disease in adults.

The first inborn error of surfactant metabolism was identified in 1993 in an infant with fatal, autosomal recessive lung disease associated with SP-B deficiency due to a frameshift mutation in the SP-B gene. More than 25 mutations of the SP-B gene have since been identified, including mutations that allow for synthesis of reduced amounts of SP-B and milder lung disease. Reduced amounts of SP-C due to an impairment of its processing from its precursor protein may also contribute to the lung disease.

The typical clinical scenario for SP-B deficiency involves a full-term neonate who presents immediately with, or who insidiously develops, severe respiratory distress with bilateral diffuse alveolar and interstitial infiltrates on chest radiograph. Surfactant therapy, especially with a preparation that contains SP-B, may result in transient improvement early in the course. Lung disease is progressive and fatal without lung transplantation. Definitive diagnosis requires finding mutations on both alleles of the SP-B gene. Infants who appear to be SP-B deficient but who do not have an abnormality in the SP-B gene have been identified. These infants may have defects in other genes, such as enzymes or other proteins important in the processing of SP-B, resulting in the same phenotype.

In a 2001 report, Nogee and co-workers described an infant who presented at six weeks of age with tachypnea and cyanosis, chest radiographic findings of increased interstitial markings, and a family history of interstitial lung disease inherited in an autosomal dominant fashion. SP-C was undetectable in the child's lung tissue. A mutation on one allele of the SP-C gene that led to production of an abnormal SP-C precursor protein was identified. It was suggested that respiratory disease occurred due to a dominant negative influence of the abnormal protein on SP-C metabolism or function. Thomas et al. reported a very large family within which autosomal dominant pulmonary fibrosis was associated with a mutation in the SP-C gene, with considerable variability in the age of onset of lung disease and lung pathology.

Nogee LM, deMello DE, Dehner LP, Colten HR: Brief report: deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med* 1993;328:406-410.

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The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Evaluate the research presented to develop a more complete understanding of the use of surfactant preparations.
- Demonstrate a more complete understanding of the advantages/disadvantages of surfactant therapy for both RDS and non-RDS diseases.
- Use the information presented herein as a basis for decision making in determining prophylaxis vs rescue use of surfactants in your clinical practice.

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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