

# Surfactant Replacement Therapy in the Neonate: Beyond Respiratory Distress Syndrome

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**Surfactant-replacement therapy is a life-saving treatment for preterm infants with respiratory distress syndrome, a disorder characterized by surfactant deficiency. Repletion with exogenous surfactant decreases mortality and thoracic air leaks and is a standard practice in the developed world. In addition to respiratory distress syndrome, other neonatal respiratory disorders are characterized by surfactant deficiency, which may result from decreased synthesis or inactivation. Two of these disorders, meconium aspiration syndrome and bronchopulmonary dysplasia, might also be amenable to surfactant-replacement therapy. This paper discusses the use of surfactant-replacement therapy beyond respiratory distress syndrome and examines the evidence to date. *Key words: newborn, prematurity, surfactant, respiratory failure, meconium aspiration syndrome, bronchopulmonary dysplasia.* [Respir Care 2009;54(9):1203–1208. © 2009 Daedalus Enterprises]**

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## Introduction

Pulmonary surfactant is a multicomponent complex of several phospholipids, neutral lipids, and associated proteins. It is secreted by the type II epithelial cells within the lung. Its major physiologic function is to reduce alveolar surface tension, confer stability to the alveoli, and maintain the alveolar surface free of liquid to facilitate gas exchange. The absence of surfactant is one of the hallmark features of respiratory distress syndrome (RDS), the most common lung disorder among infants born prematurely. Repletion with exogenously administered surfactant has demonstrated efficacy for both prophylactic and rescue approaches. To date there have been more than 40 published clinical trials evaluating the use of surfactant replacement therapy in more than 20,000 enrolled infants.

Table 1. Pathophysiologic Factors in Meconium Aspiration Syndrome

Direct toxicity of meconium constituents
Effects of inflammatory mediators
Protein leak
Surfactant dysfunction
Alveolar and parenchymal inflammation and edema
Altered pulmonary vasoreactivity
Pulmonary vasoconstriction
Effects of intrauterine hypoxemia
Airway obstruction
Altered lung elasticity

These trials showed a major reduction in both mortality and pulmonary air leaks.<sup>1</sup>

Although RDS is characterized by the absence or reduction of surfactant, there are other neonatal lung disorders in which inadequate functional surfactant may be a prominent element of the pathophysiology, either by inactivation or inhibition of synthesis. These include meconium aspiration syndrome, shock lung, pulmonary hemorrhage, pneumonia, congenital diaphragmatic hernia, and bronchopulmonary dysplasia (BPD). It seems intuitive that these disorders would be amenable to surfactant-replacement therapy. The objective of this paper is to examine the effects of surfactant-replacement therapy on two of these diseases: meconium aspiration syndrome and BPD.

### Meconium Aspiration Syndrome

Meconium aspiration syndrome continues to be a serious problem among infants born at term or beyond. It is estimated that there are 25,000–35,000 annual cases in the United States, with 30–50% of affected infants requiring mechanical ventilation. Air leaks are common, with pneumothorax reported in 15–20%. Mortality ranges from 4–7%. About two thirds of infants with persistent pulmonary hypertension of the newborn have meconium-stained amniotic fluid, and about half of the infants with persistent pulmonary hypertension of the newborn have the concurrent diagnosis of meconium aspiration syndrome.<sup>2</sup>

The pathophysiology of meconium aspiration syndrome is complex and multifactorial (Table 1). Meconium itself is a mixture of gastrointestinal secretions, sloughed intestinal epithelial cells, and potentially any substances capable of appearing in amniotic fluid, which is swallowed by the fetus. Many of these, especially bile salts, can inactivate surfactant. There is also a direct toxic effect on the lung, causing chemical pneumonitis. Inflammatory mediators, such as cytokines and eicosanoids, can also inhibit surfactant, as can the protein that leaks into the alveolar spaces.<sup>3</sup> There may be alteration in pulmonary vasoreactivity, leading to pulmonary vasoconstriction and second-

ary persistent pulmonary hypertension of the newborn. If intrauterine hypoxemia was present, there may be vascular remodeling with pulmonary hypertension. Reduced pulmonary blood flow may cause pulmonary ischemia, with damage to the type II cells and reduced surfactant production. Airway obstruction may cause increased resistance, and surfactant deficiency and parenchymal lung changes may require the use of high ventilatory support and substantial supplemental oxygen, contributing to lung injury. Thus, breaking this vicious cycle by using surfactant-replacement therapy is an attractive hypothesis. Two approaches have been attempted: surfactant replacement and surfactant lavage.

### Surfactant Replacement

Surfactant replacement is analogous to what occurs in RDS. Exogenous surfactant is administered through an endotracheal tube, generally at the same dose used in RDS. Standard surfactant preparations have been utilized.

In 1991, Auten et al published a series of 14 term infants with respiratory failure treated with surfactant-replacement therapy. Seven of these infants had meconium aspiration syndrome. Short-term benefits were demonstrated following surfactant-replacement therapy, including improved oxygenation and decreased ventilatory support.<sup>4</sup> Khammash et al subsequently reported a larger series, reporting on 49 consecutively treated term infants with severe respiratory failure; 20 had meconium aspiration syndrome. They also demonstrated improved gas exchange.<sup>5</sup>

One of the first series to examine surfactant-replacement therapy in meconium aspiration syndrome (alone) was that of Halliday et al in 1996. This retrospective review included 54 infants with meconium aspiration syndrome, who received surfactant-replacement therapy at a median age of 14 hours. The doses used varied substantially. One third of the babies required repeated doses. Overall, 18% demonstrated a significant improvement in gas exchange, 44% showed little or no response, but only two subsequently required extracorporeal membrane oxygenation (ECMO) therapy. The authors concluded that a randomized controlled trial was justified.<sup>6</sup>

A randomized controlled trial was indeed performed by Findlay and colleagues, and published in 1996. This trial randomized 40 infants with meconium aspiration syndrome requiring mechanical ventilation. Surfactant-replacement therapy was provided to 20 infants, using a 6-hour dosing interval for up to 4 doses. A slightly higher dose (150 mg/kg phospholipid) was used, compared to the dose for RDS (100 mg/kg). The investigators of that study concluded that surfactant-replacement therapy, started within 6 hours of life, improved oxygenation and decreased air leaks, severe respiratory morbidity, and length of hospital stay.

ECMO was required by 6 infants in the control group but only 1 in the surfactant-replacement therapy group.<sup>7</sup>

Lotze and colleagues undertook a large double-blind randomized controlled multicenter trial of surfactant-replacement therapy in a population of term infants with severe respiratory failure, characterized by a high oxygenation index. The surfactant-replacement-therapy group received an "RDS approach," receiving 100 mg/kg within 30 min of study entry and 3 additional doses every 6 hours (unless ECMO was required). Included in the study population of 328 were 168 infants with meconium aspiration syndrome. Although the results were not stratified for primary diagnosis, infants receiving surfactant-replacement therapy required less ECMO, without a concomitant increase in complications.<sup>8</sup>

Finally, the Chinese Collaborative Study Group for Neonatal Respiratory Diseases performed a multicenter randomized controlled trial of surfactant-replacement therapy for severe meconium aspiration syndrome. In that study, 61 patients were enrolled by 19 participating centers. Entry criteria included the clinical, radiographic, and laboratory findings compatible with meconium aspiration syndrome: birth weight > 2,500 g, postnatal age < 36 h, arterial-alveolar ratio < 0.22 and oxygenation index > 15, and mechanical ventilation for 1–2 hours with no improvement. Infants randomized to surfactant-replacement therapy received 200 mg/kg for the first 2 doses at 6–12 hour intervals. If a third and fourth dose were required, 100 mg/kg was used. Again, infants who received surfactant-replacement therapy showed statistically significant improvement in oxygenation from baseline at 24 hours, and at 3 and 7 days. There were, however, no differences in mean duration of ventilation, mortality, or major complications.<sup>9</sup>

On balance, it appears that surfactant-replacement therapy for meconium aspiration syndrome consistently improves gas exchange and short-term outcomes, especially avoidance of air leaks and the need for ECMO. It is difficult, however, to make specific recommendations, given the substantial differences in entry criteria, dose, interval, and outcome measures chosen in these trials.

### Surfactant Lavage

An alternative approach to treatment of meconium aspiration syndrome with surfactant-replacement therapy is the technique of lung lavage. This takes advantage of the detergent-like property of pulmonary surfactant, in which meconium might be solubilized and literally "washed" from the lung. Thus, in addition to repleting the lung with functional surfactant, lavage might theoretically remove particulate meconium and prevent some of the pathophysiology attributed to obstruction and toxicity.

The lavage approach appears to have been first reported by Mosca et al in 1996. This group used a combined

approach of saline lavage, followed by surfactant-replacement therapy in 2 infants with severe meconium aspiration syndrome. They instilled two 15-mL/kg aliquots of normal saline, with suctioning performed after each, followed by administration of surfactant at 100 mg/kg. Both infants tolerated the procedure and improved.<sup>10</sup>

In 1999 Lam and Yeung reported the use of surfactant lavage in 6 infants with severe respiratory failure from meconium aspiration syndrome. These babies received diluted surfactant lavage (15 mL/kg of a surfactant diluted to 25 mg/kg phospholipids). It was administered through a side port, with ventilation maintained during the procedure. These 6 infants were then compared to a historical control group of 6 patients. They concluded that surfactant lavage for meconium aspiration syndrome was safe and effective, although the only statistically significant differences between the 2 groups were duration of ventilation and duration of supplemental oxygen.<sup>11</sup>

Another anecdotal experience was reported from Japan in 2001. Three patients with meconium aspiration syndrome received 10 mL/kg of dilute surfactant lavage, followed by a standard surfactant-replacement-therapy dose. All three tolerated the procedure and improved.<sup>12</sup> A German group also did a non-randomized comparison of lung lavage ( $n = 11$ ) versus suctioning only ( $n = 7$ ) over a 12-year period. However, only the oxygenation index at 24 hours showed a statistically significant advantage to lavage.<sup>13</sup> Several other case reports or small series have also demonstrated safety and short-term efficacy.<sup>14–16</sup>

A historically controlled trial was reported from Spain in 2004. In this investigation, standard management was compared to surfactant lung lavage and to surfactant lung lavage followed by systemic treatment with dexamethasone. Both lung-lavage groups showed better short-term outcomes than standard care, and the addition of dexamethasone, a potent anti-inflammatory agent, appeared to act synergistically and improved the results, compared to surfactant lavage alone.<sup>17</sup> Given the methodology of this study, further evaluation in a randomized controlled trial seems appropriate.

The only prospective, randomized controlled trial was performed by Wiswell et al.<sup>18</sup> Infants with moderate meconium aspiration syndrome (defined by an oxygenation index between 8 and 25) were randomized to receive either standard care or lung lavage with surfactant. In this study the lavage procedure was more extensive. Three lavages were done. For the first two, each lung was separately lavaged with 8 mL/kg of a surfactant solution (2.5 mg/mL); for the last, the concentration of surfactant was increased to 10 mg/mL, but the same volumes were used. Twenty-two infants were enrolled, and 15 underwent lavage. Lavaged infants displayed (statistically nonsignificant) trends toward faster weaning from mechanical ventilation, and a more rapid decline in the oxygenation index.

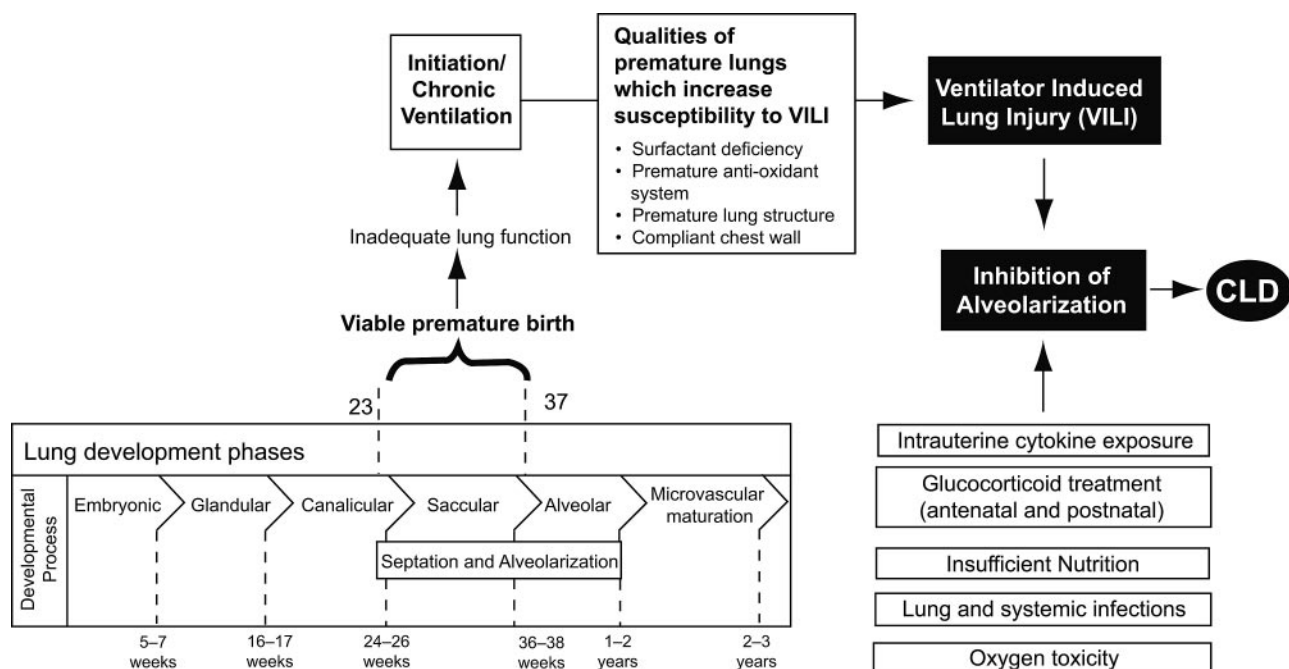


Fig. 1. Schematic diagram of the multifactorial nature of bronchopulmonary dysplasia or chronic lung disease. Preterm delivery interrupts normal lung development, and, coupled with both intrinsic and extrinsic factors, leads to diminished alveolarization and respiratory insufficiency. (From Reference 22, with permission.)

Moreover, despite the large volumes of instilled surfactant, the procedure was generally well tolerated.<sup>18</sup> A subsequent pilot trial by Dargaville et al confirmed the safety and tolerability in hemodynamically stable ventilated infants.<sup>19</sup>

Similar to the literature on surfactant-replacement therapy, it is difficult to generalize from the paucity of evidence. Nevertheless, lavage appears to be both feasible and safe if performed cautiously. There remain many unanswered questions, including surfactant concentration, dose, interval, frequency, and optimal ventilatory support. Further investigation is clearly warranted in light of the substantial problem that meconium aspiration syndrome still presents.

### Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is a term used to describe the chronic lung changes that accompany mechanical ventilation, particularly in preterm infants. It was first coined by Northway et al in 1967, describing the radiographic changes in a population of relatively late preterm babies subjected to moderate ventilatory support.<sup>20</sup> Today, affected infants tend to be more preterm and subjected to less ventilatory support, and are often described as having the “new BPD.”<sup>21</sup> The etiology of BPD is multifactorial and includes ventilator-induced lung injury (Fig. 1), inflammation, inadequate antioxidant systems, infection, ex-

posure to steroids, and inadequate nutrition, all superimposed upon a still developing lung.<sup>22</sup> Ultimately, this results in a decrease in alveolarization and can impair growth and development.

It is estimated that 30–40% of infants < 1,500 g at birth are affected to some extent,<sup>23</sup> and it is thus a considerable burden to the health-care system. Considerable investigation into ways to prevent or ameliorate BPD is underway. One of these is late surfactant-replacement therapy.

The introduction of early surfactant-replacement therapy has not altered the incidence of BPD, although this may be a demographic quirk. In other words, very preterm infants who might not have survived without surfactant-replacement therapy are now surviving, only to subsequently develop BPD. One of the interesting phenomena that has evolved is the “post-surfactant slump,”<sup>24,25</sup> where infants who had done well initially start to show increasing respiratory distress toward the end of the first week of life. It has been suggested that surfactant inactivation may be a key factor. This might be related to pulmonary edema fluid,<sup>26</sup> oxidative stress,<sup>27</sup> inflammatory mediators,<sup>28</sup> and infection.<sup>29</sup> Again, it seems that overcoming inactivated surfactant by replacing it with exogenous surfactant is an attractive hypothesis.

Indeed, as early as 1995, Pandit and colleagues published the results of a study that looked at administering a single later dose of surfactant to infants showing early chronic lung changes. Infants with birth weights < 1,500 g,

who were 7–30 days old and required mechanical ventilation and a fraction of inspired oxygen of 0.4 or more were eligible to receive a dose of surfactant at 100 mg/mL. There was no randomization or blinding. Infants served as their own controls. Ten patients were treated. Short-term improvements in supplemental oxygen requirements and a trend toward an increased ventilatory efficiency index was demonstrated.<sup>30</sup>

In 2006, Katz and Klein reported a retrospective cohort study to evaluate surfactant-replacement therapy in babies exhibiting the post-surfactant slump. They examined a group of infants with birth weights < 1,000 g consecutively admitted during the 3-year period from 1999 to 2001. Babies were assigned to one of 3 groups: no surfactant-replacement therapy; initial surfactant-replacement therapy only; and initial surfactant-replacement therapy and later surfactant-replacement therapy after day 6. Analysis of data showed that repeat surfactant-replacement therapy led to a significant improvement in hypoxemic respiratory failure and provided short-term benefit.<sup>31</sup>

Finally, a prospective randomized controlled masked multicenter trial was undertaken to address this hypothesis. Laughon et al enrolled 136 extremely preterm infants to estimate the effect of late surfactant-replacement therapy on the development of BPD. Babies were eligible if they weighed 600–900 g at birth, were 3–10 days of age, and required mechanical ventilation and a fraction of inspired oxygen of 0.3 or more. There were 34 participating centers worldwide, and stratification was by center. Babies were randomized to one of 3 groups: placebo (sham air); low-dose surfactant (90 mg/kg total phospholipids); and standard dose (175 mg/kg). Two dosages of surfactant were used because this was a pilot trial and the most effective dosage was not known. Babies were treated with up to 5 doses at 48-hour intervals, as long as they remained intubated, up to 18 days of age. Because the groups were demographically disparate, odds ratios for death or BPD were adjusted for gestational age, birth weight, and sex. Infants who received the low-dose surfactant-replacement therapy had the highest risk of death or BPD, but those who received the standard dose did the best, with an adjusted odds ratio of 0.7, compared to placebo. The investigators concluded that treatment of infants at risk for BPD with a standard surfactant-replacement-therapy dose beginning after the first 2 days of life appears to reduce the supplemental oxygen requirement for up to 48 hours after dosing and may reduce the rates of death or BPD.<sup>32</sup>

### Summary

While there is little doubt as to the efficacy of surfactant-replacement therapy to treat RDS, other conditions in the neonatal period may also be amenable to such a strategy. Surfactant inactivation and deficiency characterize

both meconium aspiration syndrome and BPD, as well as other conditions, such as pulmonary hemorrhage and pneumonia. There is still much to learn about surfactant pharmacology and pharmacokinetics, but the studies and anecdotal experiences suggest that surfactant-replacement therapy can overcome the deficiency states created by inactivation and decreased production.

Still to be determined are the best ways to administer the drug; the optimal dose, concentration, and interval; and, most importantly, the determination of the most suitable patient populations. Surfactant-replacement therapy is not inexpensive, and cost effectiveness must be included in the analysis. Finally, studies need to be designed to look at long-term outcomes as well as short-term physiologic measures.

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