

## Past, Present, and Future Perspectives on Surfactant Therapy in Neonatal Respiratory Distress Syndrome

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Surfactant therapy has undoubtedly played a central role in contributing to the remarkable advances healthcare practitioners have experienced in the management of neonatal respiratory distress syndrome (RDS) over the past few decades. Since the discovery of the relationship between surfactant deficiency and RDS in neonates by Avery and Meade in 1959,<sup>1,2</sup> and the introduction of the first surfactant products in the United States in the late 1980s and early 1990s, there has been a dramatic improvement in how the neonatal community cares for premature infants with RDS. Morbidity and mortality rates have been radically reduced, and low and extremely low birth weight babies (who would have never been resuscitated even a decade ago) now grow to be vibrant children.<sup>3</sup> Moreover, surfactant therapy is enabling practitioners to embrace noninvasive strategies such as continuous positive airway pressure (CPAP) in order to use gentler ventilation techniques associated with improved outcomes and decreased resource utilization.



Peter Gal

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At the start of my career in neonatal practice, approximately 3 decades ago, babies born at 30 to 34 weeks gestation were critical, much like our 23 week neonates today. We aggressively ventilated these babies and employed high oxygen concentrations, resulting in iatrogenic damage to the babies' lungs and eyes. Once surfactants were introduced, the babies were being oxygenated and ventilated well, ventilatory strategies started to evolve, and our survival rates were markedly improved. For example, the survival rate in 1977 for a 30-week neonate was extremely low, whereas now it is approximately 95%.<sup>4</sup>

Today, infants of 23 to 28 weeks gestation survive.<sup>4</sup> Certainly, surfactants have played a central role in these successes; however, improved strategies in terms of time of administration (i.e., in

The design of this series of papers is novel for the *Journal of Pediatric Pharmacology and Therapeutics* (JPPT). Its development

**ABBREVIATIONS** CPAP, continuous positive airway pressure; NICU, Neonatal Intensive Care Unit; RDS, respiratory distress syndrome

included contributions from a wide range of professionals involved in neonatal care such as neonatologists, pharmacists, neonatal nurse practitioners, and respiratory therapists. Further, this collection of papers will have a special distribution that will encompass a more diverse audience, which includes all members of the neonatal healthcare team.

In celebration of the uniqueness of this issues' design and distribution, we asked three individuals with distinct perspectives to describe Neonatal Intensive Care Unit (NICU) life prior to the advent of surfactants, to discuss how their careers are currently influenced by surfactant therapy, and to speculate on what they foresee in the future.

the delivery room), early extubation to CPAP, proper management of neonates on CPAP, administration of lower oxygen concentrations, and an improved understanding of the physiologic needs of the 23- to 28-weeks versus the 30- to 34-weeks neonate have all contributed to the improved morbidity and mortality rates that we are experiencing, especially in terms of RDS.

Over the course of my career, I have witnessed the metamorphosis of the children with RDS that used to follow the classic 3-day disastrous course. When we first started to use surfactants, we thought it was incredible. Then, we began to notice that approximately 20% of babies weren't doing particularly well. These infants were obviously either essentially completely surfactant-deficient or infected. What we know today is that these cases require surfactant proteins. This made an impact on me personally, and I began to examine the differences between the various surfactant preparations, specifically synthetic versus natural. Once we started using natural surfactants, we achieved some additional responses that reflected a change in our understanding of the pharmacodynamics of surfactants. Thus, we learned that all surfactants would not be equal, and the differences in pharmacodynamics would ultimately affect clinical outcomes. The pharmacodynamic differences necessitated ventilator adjustments and novel monitoring strategies which favored limiting hospital formularies to a single surfactant product. The timing of the doses was also critical and required that members of the healthcare team work together to get surfactant to patients shortly after birth. The multidisciplinary strategies needed to optimize all aspects of early management for RDS required a team effort. I have enjoyed watching our whole system collaborate to optimize care.

As for the future, I think we will continue to learn more about micro-preemies, and I believe surfactant therapy will play an important role in helping them survive. In terms of RDS, surfactants will remain a foundation for neonatal management, but healthcare providers must explore and master other adjunctive strategies such as CPAP in order to reduce serious sequelae such as chronic lung disease or intraventricular hemorrhage. Research is currently underway to manufacture less expensive surfactants, with fewer immunogenic components, administered by a less invasive delivery system; however, I believe it will be challenging to produce or create a product that will out-perform the natural surfactants currently available.



Jatinder Bhatia

**Jatinder Bhatia, MD, Chief, Section of Neonatology, Department of Pediatrics, Medical College of Georgia, Augusta, Georgia**

Prior to the advent of surfactant therapy, neonatologists had to go through a 3- to 5-day period of intensive treatment, with many deaths and sequelae. Once surfactants were introduced and I became adept at using them, we no longer saw the same intense disease process. Instead, we actually witnessed a shortened course of therapy and produced healthier babies, although the incidence of chronic lung disease remained a concern.

As surfactants have been refined and improved, we are now actually witnessing an even more remarkable effect on our neonates. This is exciting for neonatologists because prior to surfactants, the very micro preemie was not even resuscitated. Now that we have surfactants available, in combination with changes in our thinking process, we have started to save younger and younger babies, and continue to redefine the limit of viability. Moreover, with the wide-spread use of surfactants available today, the newer generation of practitioners and healthcare providers do not even know what a pre-surfactant baby looks like. What we are doing now is moving towards aggressive surfactant therapy, taking the babies off the ventilator earlier and trying to decrease the incidence of chronic lung disease.

For the future, we need to improve on CPAP devices and train healthcare professionals to perform CPAP properly, because it is not easy—it takes a lot of dedication. I also think that we will attain more understanding about the immunologic benefits of surfactant and explore different ways of giving surfactant, aerosol surfactants for example, so that we can avoid intubating babies. If we can make these advances, then we can really make an impact on neonates and chronic lung disease.



Kim Oski

**Kim Oski APRN, neonatal nurse practitioner at the University of Connecticut NICU, Farmington, Connecticut**

In the pre-surfactant era, survival was questionable for the premature infant. In order to provide adequate ventilation and oxygenation, we employed high ventilator settings and prolonged ventilator support. The neonates had long hospital stays, and we encountered the need for chest tubes due to air leaks in addition to ventilator dependency that often required tracheostomies. Unfortunately, these techniques and procedures resulted in a substantial amount of chronic lung injury.

I participated in one of the inaugural surfactant studies, and I recall being very happy when the trial was halted early. The trial was supposed to be blinded, but we all knew without a doubt which neonate received the surfactant and which neonate received the placebo—you could immediately see the difference in ventilator support and the weaning of oxygen between treated and untreated babies. In fact, the trial was really hard to endure at times, especially when working with twins and only one twin received the surfactant.

Surfactants have changed the practice of neonatology. Today, we are better able to manage respiratory issues and co-morbidities in our neonates. We are able to transition them from ventilators to CPAP or nasal cannula quicker, thereby attempting to decrease the incidence and severity of chronic lung injury. While morbidity rates of BPD are still high, BPD severity is decreased, and these infants are now treatable.

I recall one family who had tried for years to have children and who had finally given birth to twins at 24 weeks gestation. While one was lost at birth, we resuscitated the other twin and administered surfactant; that twin is now a happy, healthy two-year-old girl. It is just wonderful to see how much the parents love their child, how lucky they all are, and if it weren't for surfactant, this couple would likely be childless. This story is not unique; however, it portrays the personal impact that surfactants have made on my life.

While we have not yet experienced the decrease in morbidities that we would like, surfactants have certainly had a positive outcome on neonates in general. In the future, we would love to see infants without intraventricular hemorrhage, ocular, and auditory issues. We would also like to see further decreases in the incidence and severity of RDS. Perhaps we could improve outcomes even further if we can enhance the effectiveness of surfactants, or surfactant protein B, maximize our understanding surrounding dosing intervals and ideal dosages to be administered, and modify our delivery techniques to include aerosol products.

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This issue of JPPT contains four outstanding articles. The series of papers commences with a manuscript by Rangasamy Ramathan, MD, (Keck School of Medicine, University of Southern California) focusing on the use of surfactants in the management of RDS in the extremely premature neonate. This article is followed by a discussion of CPAP

by Kris Sekar, MD, (Oklahoma University Health Science Center, Oklahoma City, OK). The third contribution by Liza Barbarello-Andrews, PharmD, (Ernst Mario School of Pharmacy, The State University of New Jersey, Piscataway, NJ) and Wallace Marsh, PhD, MBA, (Shenandoah University, School of Pharmacy, Winchester, VA) presents an in-depth overview of the pharmacoeconomic aspects of surfactant therapy. The supplement's closing manuscript examines surfactant selection criteria and practical issues involved with surfactant therapy. Presented in a question and answer format, this practical article was designed based on a roundtable discussion involving Karen Corff, MS, APRN, NNP and

Debra McCann, MS, ARPN (both from Oklahoma University Health Sciences Center, Oklahoma City, OK), Richard Williams RRT, NPS (Neonatal-Pediatric Clinical Consultant, St. Petersburg, FL), and Steve Greubel, RRT, AS (St. Mary's Hospital for Women and Chil-

dren, Evansville, IN).

It is the aspiration of all involved that this issue of JPPT will prove to be both stimulating and provocative and will provide valuable information to help further best practices in the evolving realm of neonatal medicine.

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Editor*

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