

## Controversies in the Management of Respiratory Distress Syndrome in Premature Neonates

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Current practices have lowered morbidity and mortality in premature infants over the past two decades. This improvement in outcomes is associated with regionalization of antenatal obstetrical management of potential preterm deliveries by referrals to centers with high-risk obstetricians and Neonatal Intensive Care Units (NICUs), timely administration of antenatal steroids before delivery [1-3] and improving neonatal intensive care strategies. Nonetheless, Respiratory Distress Syndrome (RDS), due to surfactant deficiency, continues to be a major cause of morbidity and mortality in the United States. Neonatology is a relatively new subspecialty in which clinical strategies frequently are not supported by the robust evidence based data found in other specialties. Thus, NICU strategies tend to change rapidly and it is difficult for the clinician to keep abreast of the new information. This Special Edition of the Journal of Pulmonary and Respiratory Medicine is created to provide the general pediatrician and practicing clinical neonatologist with an update of the state on the art care of RDS in the NICU.

RDS is a multisystem disease that requires a multifaceted approach to improve outcomes. These strategies begin in the delivery room, extend to the NICU management and continue in the outpatient management of survivors. The Special Edition provides an update to the current thought regarding clinical and basic research that may be invoked to provide the best clinical care to our most fragile patients. Bringing treatment of RDS from laboratory to bedside [4,5] and beyond has made this an exciting project. We believe that pediatricians who care for neonates will find this series of review articles intriguing, even if you do not agree with all that is written. I hope that the pediatric residents rotating through our NICUs will find these articles a useful introduction to the management of premature babies with RDS. There is some obligatory redundancy in the various reviews, arising from the different perspectives of the individual authors, all practicing clinicians.

There are many controversies and uncertainties regarding optimal management of premature infants with RDS, beginning with choosing the best strategy of respiratory support in the delivery room. The next controversy surrounds the use of surfactant therapy, which surfactant, what dose, how many doses, and how and when it should be administered. Comparisons of available animal derived surfactant preparations is incomplete, but there appear to be benefits to a rapidly acting, animal-derived surfactant with a high concentrations that allows a large initial dose, 200 mg/kg, twice the dose of other surfactant preparations [6-8]. This is concordant with the observation that two doses of surfactant are better than a single dose in the treatment of patients with severe respiratory distress syndrome [9,10]. Even with use of surfactant, variations in respiratory management of patients with RDS result in profoundly different rates of bronchopulmonary dysplasia [11-13]. A review of the multitude of mechanical ventilation strategies and the withering array of new terms to describe available ventilation strategies is presented. A review of the newer strategies of Non-Invasive Positive Pressure Ventilation is also presented, as it appears that mere placement of an endotracheal may increase the frequency of chronic lung disease [14]. The contribution of the cardiovascular system in the management of RDS is reviewed. The cardiovascular effects of RDS treatment represent a poorly studied clinical area. Regional hemodynamic responses to RDS and its treatment in premature infants may cause unanticipated changes in cerebral, PDA and intestinal blood

flow. Surfactant type and volume and administration protocols as well as permissive hypercapnea may have profound hemodynamic effects [15-17]. The change in our views regarding management of a PDA in premature infants is now extremely controversial and is reviewed in detail. We may no longer need to treat most infants with PDAs and the treatment may, in fact be detrimental [18,19]. Clearly more clinical research is needed.

Management of extremely premature infants with chronic lung disease after discharge from the NICU is an even more controversial topic where the management strategies of the NICU and the outpatient pulmonologist may conflict. For example, while use of systemic corticosteroids clearly improves lung function, the therapeutic cost of neurotoxicity makes it an unacceptable routine therapy [20]. Nonetheless, steroid treatment for infants with severe RDS with evolving chronic lung disease and for certain outpatients, steroid management of chronic lung disease is sometimes indicated. Furthermore, infants with pulmonary hypertension and bronchopulmonary dysplasia represent a very high risk population of NICU graduates [21,22]. It is unclear whether continued supplemental oxygen therapy sufficient, or should other strategies be initiated.

We have not attempted to address the efficacy of adjunct therapies, e.g. Superoxide Dismutase (rhSOD) and Clara Cell Secretory protein (rhCC10) for the treatment of RDS and prevention of BPD [23-25]. These new drugs are currently not available for use in the United States and, while promising, do not have adequate supportive clinical trials data to recommend routine use. Clinical trials for rhCC10 are ongoing.

We hope that this series of reviews will inform and stimulate discussion amongst neonatologists and pediatricians who care for neonates and graduates of NICUs. In addition, since the World Health Organization has recently added surfactant to the list of essential medicines for developing countries, a timely review of current strategies utilized in the United States may be beneficial to pediatricians new to the management of RDS in premature babies.

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