Long-Term Respiratory Morbidity in Preterm Infants: Is Noninvasive Support in the Delivery Room the Solution?

The adverse long-term pulmonary consequences of extreme prematurity are increasingly recognized. Seminal work in animals suggests that lung injury likely starts during the moments after birth.[1,2] Therefore, much subsequent clinical research has focused on optimizing the initial resuscitation and stabilization of the extremely preterm infant. Two articles in this issue of *The Journal* provide insight into how delivery room (DR) practice may be improved and may influence the short- and long-term outcomes of preterm infants.[3,4]

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In survivors of prematurity, spirometry at school age consistently demonstrates decreased lung function compared with full-term controls.[5-10] These deficits are more severe in extremely preterm infants with bronchopulmonary dysplasia (BPD). Worse, such effects persist throughout childhood and likely into adulthood.[11-13] In addition to the known impact of prematurity on long-term respiratory morbidity, BPD is an independent predictor of neurodevelopmental outcomes at 18 months.[14] Similarly, duration of ventilation beyond 60 days is correlated with developmental impairment at 18 months.[15] Thus, strategies to prevent lung disease of prematurity and its associated long-term sequelae are needed.

Although neonatologists have recognized the potential impact of DR interventions on the outcomes of preterm infants for some time, such interventions have only recently been studied systematically in large randomized trials. Several trials have evaluated the use of continuous positive airway pressure (CPAP) in comparison with immediate intubation and surfactant administration.[16-18] These individual studies show trends toward decreased rates of death or BPD and reduced need for surfactant with the use of noninvasive support, but no significant differences. This is likely due to individual trials being underpowered to identify this treatment effect because three pooled analyses including over 3000 infants demonstrate that strategies aimed at avoiding early mechanical ventilation in preterm infants have a "small but significant beneficial impact" for the prevention death or BPD.[19-21] Although these analyses differ in significant details, they consistently report a significant reduction of death or BPD in infants treated with CPAP, with a number needed to treat (NNT, 25-35 infants treated with CPAP prevents 1 case of BPD). This NNT is higher than the NNT to prevent BPD for caffeine (10) and Vitamin A (12),[22] but given the relative safety of CPAP, these data provide a sound rationale for prioritizing non-invasive respiratory strategies in extremely premature infants. Such evidence led the American Academy of Pediatrics Committee on Fetus and Newborn to publish a policy statement in January 2014 concluding that "the early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death compared with treatment with prophylactic or early surfactant therapy."[23]

In this issue of *The Journal*, Stevens et al report the Breathing Outcomes Study, which evaluated parental reports of respiratory outcomes over the first 18-22 months of life among participants in the National Institute of Child Health and Human Development Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT).[3,17,24] The previously reported SUPPORT compared DR CPAP with routine intubation and high to low oxygen saturation targeting in extremely preterm infants.[17,24] The Breathing Outcomes Study showed no difference in the primary outcome of wheezing during the worst 2-week period or cough lasting more than 3 days (without a cold) by 18-22 months corrected age among any of the groups of SUPPORT.

Because each individual trial of DR CPAP appears to show only modest results and meta-analyses report large numbers needed to treat, it is reasonable to question why noninvasive respiratory support in the DR has not thus far had more impact in limiting lung disease in preterm infants. We suggest several potential explanations for the modest effect of a noninvasive DR strategy. First, the most effective methods of performing noninvasive respiratory support to avoid intubation in the DR setting remain unclear. Although these trials were designed to compare CPAP vs routine intubation and surfactant administration, many premature infants require positive pressure ventilation (PPV) during their initial stabilization after birth. Performing PPV in extremely low birth weight infants is difficult: facemask leak, airway obstruction, and inability to accurately assess chest wall movement are common problems, resulting in variable tidal volume delivery.[25,26] Many extremely preterm infants are not well stabilized with noninvasive PPV after birth, and then require

BPD	Bronchopulmonary dysplasia
BPM	Beats per minute
CPAP	Continuous positive airway pressure
DR	Delivery room
HR	Heart rate
NNT	Number needed to treat
PPV	Positive pressure ventilation
SUPPORT	Surfactant Positive Airway Pressure and Pulse Oximetry Trial

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tracheal intubation to achieve effective ventilation.[27] Thus, in these trials, many infants assigned to CPAP were intubated within the first minutes of life for failed noninvasive resuscitation. For example, in SUPPORT, one-third of infants assigned to the CPAP arm were intubated in the DR for resuscitation.[17] This co-intervention potentially diluted the observed treatment effect of a noninvasive strategy.

Investigators have sought to improve the technical aspects of delivering noninvasive support (both CPAP and PPV) during DR resuscitation by studying alternate resuscitative devices,[28] between device and infant,[29,30] and respiratory function monitors in the DR.[31] Although the Neonatal Resuscitation Program and the International Liaison Committee on Resuscitation have made considerable strides in standardization of neonatal resuscitation, recommendations remain cautious in some areas, including choice of apparatus.[27,32] For instance, the Neonatal Resuscitation Program gives some guidance about the choice of T-piece vs self-inflating bag for administering PPV, but has not firmly advocated one modality. This is because until now, studies did not demonstrate clear superiority in any given method of administering noninvasive support. However, also in this issue of *The Journal*, Szyld et al report a large, international, cluster-randomized crossover study in newborns ≥26 weeks gestation requiring PPV after birth, comparing the safety and efficacy of the T-piece resuscitator with the self-inflating bag.[4] Although no difference was observed between treatment arms with respect to the primary outcome of the proportion of infants with heart rate (HR) ≥100 beats per minute (BPM) at 2 minutes of life, infants randomized to the T-piece arm were intubated less frequently than infants in the self-inflating bag arm (17% vs 26%, $P = .002$). Provocatively, in a post hoc exploratory analysis of very low birth weight infants, subjects treated with the T-piece were significantly more likely to have a HR ≥100 BPM at 2 minutes of life, less likely to be intubated for ventilatory support, and less likely to develop BPD (25% vs 40%, $P = .036$).

An additional problem of existing studies of DR interventions may be the choice of outcomes caught between two extremes, which we might label "proximate but largely surrogate" and "distant but clinically relevant." Potentially useful outcomes of vital sign stability, such as HR ≥100 BPM at 2 minutes of life (the primary outcome in the Szyld trial), are often unavailable from cardiac or pulse oximeter monitors in the first minutes of life,[33] and may be inaccurate when made by clinical assessment.[34] Outcomes related to the need for further interventions (ie, need for intubation or increased supplemental oxygen) are prone to clinician preference, unless clearly defined by criteria. Further, it is unclear which of these short-term outcomes are associated with improvement in long-term respiratory outcomes.

Despite its virtues, even the intermediate-term outcome of BPD has limitations. BPD is most frequently diagnosed by either an oxygen requirement or failure of an oxygen reduction test at 36 weeks corrected age.[35-37] As we have argued above, the diagnosis of BPD clearly correlates with long-term respiratory and developmental outcomes. At the same time, many preterm infants without a diagnosis of BPD also experience clinically important respiratory morbidity throughout childhood and beyond. Therefore, longer-term outcome measures may be more clinically relevant. In secondary analyses, Stevens et al report that infants who received CPAP instead of intubation and mechanical ventilation had less respiratory morbidity up to 18-22 months corrected age, including fewer episodes of wheezing without a cold, fewer diagnoses of respiratory illness by a doctor, fewer doctor or emergency room visits for breathing problems, and less impact of respiratory disease on the family.[3] Although BPD predicted nearly all respiratory morbidities, there were still high rates of these outcomes even among infants without BPD. For example, 49% of children without BPD were diagnosed with asthma, reactive airway disease, BPD flare-up, bronchiolitis, bronchitis, or pneumonia, and 26% had to stay in the hospital overnight for wheezing or breathing problems during the first 18-22 months of life. Perhaps such outcomes are ultimately more important to the patient and family than the diagnosis of BPD.

Are we improving respiratory outcomes with the use of noninvasive support in the DR? Can these benefits be boosted? In keeping with the prior literature, the studies by Stevens et al and Szyld et al in this issue of *The Journal* show further evidence of the benefits of noninvasive support in the DR. Together, these studies add to the existing literature suggesting that the trajectory of respiratory morbidity in some preterm infants may be modified by both the use and the quality of noninvasive DR respiratory support. Future research is critical to further decreasing the incidence of long-term respiratory morbidity after premature birth. Initial studies of sustained lung inflation, a novel method of recruiting the lung and establishing a functional residual capacity after birth, show early promise[38,39]; larger randomized trials are needed to determine the impact of this intervention on long-term respiratory morbidity. Studies such as the Sustained Aeration of the Infant Lung Trial will continue to advance our understanding of how to optimize noninvasive support,[40] whereas studies such as the Prematurity and Respiratory Outcomes Program are poised to develop improved definitions of BPD that will better correlate with clinically important longer-term respiratory outcomes.[41] However, it is unlikely that even optimally delivered noninvasive support in the DR will be the only solution to this problem. Ultimately, we are likely to find that properly delivered noninvasive respiratory support is just one critical element in a series of therapies that together will minimize the adverse long-term consequences of extreme prematurity. ■

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