Continuous Positive Airway Pressure to Prevent Neonatal Lung Injury: How Did We Get Here, and How Do We Improve?

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Supporting the respiratory status of the newly born, critically ill premature neonate is a long held focus of the practicing neonatologist. One could argue that neonatology evolved out of the search for the pathophysiology of respiratory distress syndrome (RDS); and that it was defined by interventions aimed at preventing and treating RDS, namely antenatal corticosteroids (ACS) and surfactant treatment. There are now multiple interventions to assist the premature infant during this transition including ACS, surfactant, monitored administration of supplemental oxygen, and sophisticated mechanical ventilators. With these advances, neonatology has witnessed an improvement in survival of the smallest, most premature neonates and pushed the threshold of viability to ~22 weeks' gestational age (GA). With improved survival of these infants, clinicians are now asking "Can we improve serious morbidities such as bronchopulmonary dysplasia (BPD)?" Infants diagnosed with BPD are at higher risk of poor pulmonary and neurodevelopmental outcomes. Recent randomized controlled trials (RCTs) consistently demonstrate that early, routine use of nasal continuous positive airway pressure (CPAP) can decrease BPD. However, the treatment effect is small, which may be related to the high rate of CPAP failure resulting in a need for mechanical ventilation. Nonetheless, reducing CPAP failure might enhance efficacy of CPAP therapy to prevent BPD. Here, we review the evidence that supports routine use of CPAP to prevent neonatal lung injury. We discuss criteria to define CPAP failure, and review both proven and emerging therapies to optimize successful implementation of CPAP.

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BPD and Its Associated Morbidities

In 1967, Northway coined the term BPD to describe the clinical, radiographic, and pathologic characteristics of premature infants that had received mechanical ventilation and supplemental oxygen.[1] In 2000, a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Workshop proposed the current definition of BPD to incorporate the nodal 36-week time point suggested by Shennan.[2] This severity based definition applied at 36 weeks' postmenstrual age (PMA) includes 3 categories of disease (mild, moderate, severe) in infants born less than 32 weeks' gestation.[3] More recently, a room-air challenge at 36 weeks' PMA was added to make the diagnosis more objective and less susceptible to local practice variation.[4,5] With the increased use of noninvasive positive pressure support (eg, high flow nasal cannula) to deliver room air, up to 2.1% of babies cannot be classified using the current NICHD Workshop definition.[6] As there is no established consensus on how to treat a baby diagnosed with BPD, perhaps the most important reason to make the diagnosis is to provide prognostic information to parents and healthcare providers. Thus, it is critical that the diagnosis of BPD accurately predicts poor long-term pulmonary and neurodevelopmental outcomes.

The diagnosis of BPD only requires a GA, a PMA, and the respiratory course of the infant.[3] The ease of making the diagnosis makes it attractive for both clinical practice and research studies. However, some have argued that the low sensitivity and specificity of BPD to predict poor respiratory and neurodevelopmental outcomes limits its prognostic value.[7,8] In a follow-up study of babies enrolled in the trial of indomethacin prophylaxis in preterms, the accuracy of BPD (defined as supplemental oxygen at 36 weeks' PMA) to predict poor pulmonary or neurosensory outcome was only 63%.[9] However, the ability of BPD to predict outcomes improves with the use of the 2000 NICHD severity-based definition.[10] Furthermore, although BPD is not a perfect predictor of long-term outcomes, multiple studies have shown it is associated with long-term pulmonary functional abnormalities and poorer neurodevelopmental outcomes.[11-13] This suggests that it is reasonable to expect that preventing lung injury in the

ACS	Antenatal corticosteroids
BPD	Bronchopulmonary dysplasia
COIN	Continuous Positive Airway Pressure or Intubation at Birth
CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
GA	Gestational age
INSURE	Intubate, surfactant, extubate
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
SLI	Sustained lung inflation

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extremely preterm neonate will improve the long-term pulmonary and neurodevelopmental outcomes.

Can We Improve Mechanical Ventilation?

Despite advances in neonatal care, the burden of BPD has remained relatively stable.[14,15] The Neonatal Research Network recently reported the outcomes of over 34 000 infants born at 22-28 weeks' gestation between 1993 and 2012.[15] Disappointingly, the incidence of BPD increased over this interval from 32%-47%, disproportionally affecting those born at the earliest GAs (<26 weeks' GA).[15] Of note, over 85% of the infants in this cohort were exposed to mechanical ventilation.[15] Furthermore, prolonged ventilation is one of the strongest and most important risk factors for poor neurodevelopmental outcome.[16,17] These data stress the importance of approaches aimed at minimizing neonatal lung injury by using less invasive modes of respiratory support.

In 1975, Philip[18] proposed that the duration of supplemental oxygen and positive pressure support contributed to the pathophysiology of BPD. Since that time, laboratory and clinical data have shown us that BPD is a multifactorial disease.[19] However, the list of factors contributing to lung injury, specifically related to respiratory support, has grown to include volutrauma, barotrauma, atelectrauma, rheotrauma (inappropriate airway flow), and biotrauma.[20,21] Experimental studies support a role played by mechanical ventilation in the pathogenesis of lung injury.[22] Furthermore, clinical data support a relationship between exposure to mechanical ventilation and an increased risk of developing BPD.[23-29] Therefore, implementing lung protective strategies to avoid the complications of mechanical ventilation might minimize lung injury.

Unfortunately, current "new approaches" to invasive mechanical ventilation do not appear to minimize lung injury and prevent BPD. For example, high frequency ventilation does not reduce the incidence of BPD in the smallest, high-risk babies.[30-33] Volume-targeted ventilation still remains promising, but numbers randomized have been few.[34,35] Newer approaches, including neutrally adjusted ventilator assist, have not been adequately studied to support their widespread use in the neonatal intensive care unit (NICU).[36,37] Perhaps our inability to find a "better" modality of invasive mechanical ventilation to limit lung injury and prevent BPD may indicate that a "better" modality does not exist. The reality may be that the developing human lung at 22-26 weeks' gestation is uniquely susceptible to injury caused by invasive mechanical ventilation. If this is true, reducing the burden of BPD will come only with limiting the exposure to invasive mechanical ventilation.

If Improving Mechanical Ventilation Is Not the Answer, Can We Do Less of It?

In 1971, Gregory reported the use of CPAP delivered via endotracheal tube or head box to treat RDS in neonates.[38] Shortly thereafter, easier noninvasive delivery of CPAP using either a facemask or binasal prongs was reported.[39,40] Experience with CPAP in the NICU grew, and it was shown to be a powerful tool in preventing extubation failure.[41] However, CPAP was not used widely as a primary means of respiratory support. In 1987, Avery et al[42] reported a significantly lower rate of BPD (defined as oxygen therapy at 28 days) in very low birth weight infants treated at Columbia University when compared with 7 other similar centers.[42] The early and aggressive use of CPAP was highlighted as a potential important contributor to the lower incidence of BPD. This was followed by clinical reports suggesting that avoiding intubation decreased the risk of developing BPD, but data from RCTs were lacking.[29,43]

Concurrent with these clinical reports, multiple RCTs demonstrated that the use of prophylactic or "early surfactant" in at-risk, preterm infants decreased air leak and improved survival.[44,45] Based on these results, prophylactic surfactant became the standard of care for babies at high risk of developing RDS and lung injury.[46,47] Importantly, these studies included very few extremely preterm infants and were performed in an era when many babies did not receive antenatal steroids.[44,45] Furthermore, infants receiving surfactant were compared with "control," mechanically ventilated infants, leaving the effectiveness of noninvasive support understudied. Therefore, as the use of ACS increased, and smaller babies survived, it remained unknown whether prophylactic surfactant, compared with noninvasive support, provided the same benefits to that group of patients.

With this in mind, and only much later, 3 large RCTs were performed in an attempt to answer a specific question: In preterm infants at high risk of lung injury (<30 weeks' GA), does routine use of CPAP, compared with routine intubation and prophylactic surfactant, prevent BPD?[48-50] Importantly, in the Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial, babies that were randomized to intubation did not routinely receive surfactant.[49] Thus, only 2 RCTs have directly compared the use of CPAP as a primary means of respiratory support with routine intubation and prophylactic surfactant in preterm infants at high risk of lung injury (<30 weeks' GA).[48,50] Both those studies had high rates (>90%) of ACS use. Taken together, these data demonstrate that routine use of CPAP significantly reduces the combined outcome of BPD (assessed at 36 weeks' PMA) or death in at-risk preterm infants, with a number needed to treat of 17.7 (**Figure 1**; available at www.jpeds.com). Furthermore, pooled data from these 2 trials showed that a trial of CPAP in extremely premature infants is safe. However, it is disappointing that routine use of CPAP does not provide a larger treatment effect; the incidence of BPD alone, in survivors born at <28 weeks' GA, remains unacceptably high at ~40%.[48,50] It is reasonable to ask