

## Bronchopulmonary Dysplasia: Executive Summary of a Workshop

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**D**espite significant advances in perinatal care, bronchopulmonary dysplasia (BPD) remains one of the most common, complex, and intriguing diseases in perinatal medicine. The pathogenesis of BPD remains to be elucidated fully. Defining this disease continues to be imprecise and varies across institutions, and evidence-based guidelines addressing management are lacking. To address these and other knowledge gaps, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) held a workshop on BPD in October 2016. Information presented at the workshop included an overview of BPD providing a definition, epidemiology, pathogenesis pathways, and the strengths and limitations of available management options. The expert panel also discussed a research agenda; the use of advanced technology including medications, respiratory support measures, modern imaging, and management for preventing and treating BPD; and the current approach to the follow-up of these infants. The workshop panel developed a proposal for an updated definition for BPD based on prior definitions and current care practices. This report provides a summary of the workshop proceedings.

BPD was first described in 1967 by Northway et al in an era when the mortality from respiratory distress syndrome (RDS) was >50%.<sup>1</sup> Infants who were ventilated and survived the initial phase of RDS often recovered slowly from their pulmonary injury. Northway et al reported the stages of lung injury progression.<sup>1</sup> The authors named the disorder, BPD, a chronic disease with a “prolonged healing phase” of RDS. Oxygen toxicity, positive pressure ventilation, and endotracheal intubation were all implicated as causative factors for the development of BPD. Later, injuries from mechanical ventilation (“ventilator-induced lung injury”) captured by the catch phrase—“pressure + volume + time”—was emphasized<sup>2,3</sup> as causative factors for BPD. Initially, researchers included radiologic features and pathologic findings when available to define BPD. As the survival rate of RDS increased with more BPD survivors, a clinical definition for BPD was adopted as “those infants requiring supplemental oxygen on post-natal day 28.” As more

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immature infants survived, it was felt that day 28 oxygen use could be related to other factors (eg, prematurity) and in 1988, Shennan et al refined the definition to oxygen use at 36 weeks postmenstrual age (PMA).<sup>4</sup>

In 2000, a workshop sponsored by the National Heart, Lung and Blood Institute proposed a more comprehensive definition for BPD to help identify varying severity and, thus, they categorized BPD as “none, mild, moderate or severe.”<sup>5</sup> “No BPD” was defined as <28 days of supplemental oxygen. Mild BPD included infants who received oxygen or respiratory support for >28 days but were on room air at 36 weeks PMA. Infants with moderate BPD required supplemental oxygen, <30% fraction of inspired oxygen concentration, at 36 weeks PMA. Finally, severe BPD was classified as the use of >30% oxygen or positive pressure at 36 weeks PMA. After the National Heart, Lung and Blood Institute workshop, a further refinement in the definition included a physiologic challenge of supplemental oxygen withdrawal to test for oxygen need at 36 weeks PMA.<sup>6</sup> Infants were classified as “Yes BPD” by the “Physiologic definition of BPD” if they had an oxygen saturation of <88% within 60 minutes of a “room air challenge test.” Subsequently, the saturation target was

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increased to <90%.<sup>7,8</sup> More recently, the Canadian Neonatal Network evaluated the definitions of BPD that were commonly used for epidemiology and clinical trial outcomes for predictability of lung disease and neurodevelopmental injury at 18-21 months of age and found that oxygen and/or respiratory support at 40 weeks PMA best predicted ongoing respiratory morbidity at 18-24 months of age.<sup>9</sup> A limitation of using this later time point is that many infants are discharged from the hospital before 40 weeks PMA. Further, changes in neonatal respiratory support clinical practices including the use of high-flow nasal cannula with room air (21% oxygen) or very low flow with 100% oxygen make many infants unclassifiable by current standard BPD definitions.<sup>10</sup> An attempt to compare various BPD definitions is worthwhile to establish which ones can more precisely predict long-term outcomes in babies discharged from the initial hospital stay.

The relationship between the definitions of BPD used for trials—typically oxygen use at 36 weeks PMA—and longer term outcomes have been inconsistent. For instance, decreased forced expiratory flows measured at 6 and 18 months using infant lung function techniques have not been associated with BPD.<sup>11</sup> However, others have demonstrated that airway obstruction assessed during infancy is worse in those with BPD compared with those without this diagnosis.<sup>12</sup> Furthermore, recent studies that show BPD is predictive of respiratory outcomes during the first 1-2 years of life.<sup>13</sup> BPD is currently believed to result from the combination of developmental immaturity, injury, inflammation, repair, and healing. Updates and modifications to the definition of BPD are necessary, given the changes in the neonatal preterm patient population as well as neonatal intensive care unit (NICU) clinical practices over time.

## Epidemiology and the Current Problem of BPD

BPD affects 10 000-15 000 infants annually in the United States.<sup>14</sup> Approximately 40% of extremely low birthweight infants (birthweight of <1000 g) develop BPD.<sup>15</sup> Unlike other morbidities complicating severe prematurity, the incidence of BPD did not consistently decrease in the Vermont-Oxford Database from 2005 to 2014<sup>16</sup> or in the NICHD Neonatal Research Network over a 20-year period.<sup>15</sup> BPD remains a persistent problem in part because advances in neonatal care have improved the outcomes and survival of the smallest infants who more frequently develop BPD; as survival increases, one might predict that BPD might also increase.

The natural history of BPD into early childhood is poorly understood. Infants at risk for BPD have changed over the past several decades; smaller, more immature infants are at greatest risk. There is an urgent need for data that better describe the clinical progression and resolution of BPD over time. The Prematurity and Respiratory Outcomes Program (PROP)<sup>10,17-19</sup> collected data on infants born at <29 weeks of gestation from birth through 1 year of age, focusing on the evolution of lung disease and respiratory outcomes. Registries with follow-up through school age will collect data concerning later respiratory morbidities, hospitalizations, and the economic impact

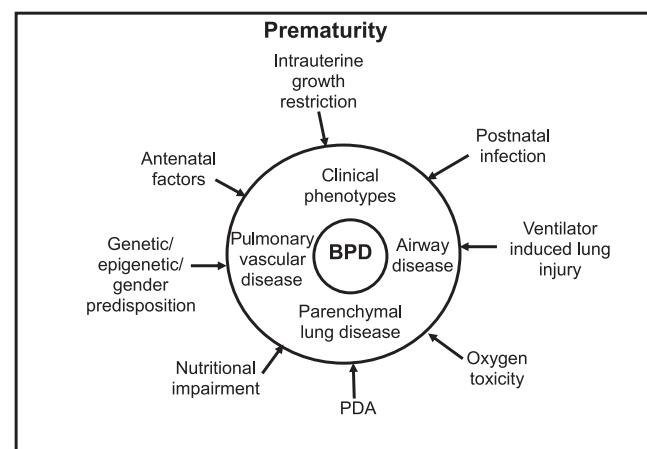
of BPD, thereby defining potential outcomes for clinical trials. Advanced imaging also has the potential to shed light on contributing factors and disease progression.<sup>20-22</sup> There is clearly a need for integrated, multidisciplinary research and clinical teams, both in the NICU and for the longer term follow-up of these infants.<sup>23</sup> One positive outcome of PROP has been the “cross-talk” among various disciplines, including neonatologists and pediatric pulmonologists.

## Lung Development and BPD

Lung development includes the embryonic, pseudoglandular, canalicular, saccular, and alveolar stages; alveolar growth and differentiation must continue postnatally for preterm infants. An extremely preterm birth can significantly impair alveolarization and normal lung growth, even without supplemental oxygen exposure or mechanical ventilation.<sup>24</sup> Even breathing room air results in significantly higher oxygen exposure to the developing lung compared with that encountered in utero. Infants at the greatest risk for developing BPD (ie, <30 weeks of gestation) are often exposed to supplemental oxygen in the late canalicular or saccular phases of lung development. The role of genetic factors, intrauterine and postnatal inflammation and infection, oxidant stress, and NICU care strategies in disrupting lung development continue to be defined. A model that integrates the perinatal risk factors for BPD is shown in the Figure.

## Prevention and Early Interventions for BPD

The most effective strategy to prevent BPD is to avoid extreme preterm birth. However, if preterm birth is inevitable,



**Figure.** Multifactorial etiology of BPD: different antenatal and postnatal factors contribute to BPD. The clinical phenotypes and severity of BPD can vary between subjects with variable contributions from parenchymal lung disease, airway disease, or pulmonary vascular disease. The degree of prematurity is the most important predisposing factor.

attention needs to be given to maternal and early postnatal interventions that could decrease the risk or severity of BPD in extremely preterm infants. It was felt by the workshop panel that to truly "prevent" BPD, interventions would have to occur prenatally, or within a short time after birth (eg, 7 days). Antenatal corticosteroid therapy can improve lung maturity and reduce neonatal mortality and complications.<sup>25</sup> Antenatal corticosteroid therapy has been reported to decrease mortality rates in 23- to 25-week gestational age infants; however, survivors have higher rates of BPD.<sup>26,27</sup> Intrauterine growth restriction is a major risk factor for BPD; the prevention of intrauterine growth restriction may be 1 path to decrease the rate of BPD.<sup>19,28,29</sup>

The impact of maternal smoking on lung function and health include decreased forced expiratory flows, decreased passive respiratory compliance, increased hospitalization for respiratory infections, and an increased prevalence of childhood wheeze and asthma.<sup>30</sup> Maternal interventions aimed at smoking cessation or modification of the deleterious effects of nicotine may be targets for the improvement of respiratory outcome. Vitamin C supplementation administered to pregnant women can reduce wheezing at 1 year of age in newborns whose mothers were smokers.<sup>31</sup> Maternal smoking was also identified as a postdischarge factor that was independently associated with later respiratory morbidity in the first year of life.<sup>19</sup>

Potential opportunities for delivery room and early life interventions to prevent BPD include delayed cord clamping or cord milking, less invasive modes of surfactant administration, gentle ventilatory approaches including sustained inflation, positive end-expiratory pressure, and using respiratory function monitors to guide care in the immediate postnatal period. Respiratory function monitors can include measurements of pressure, flow, and volume. There is further need for device development for the delivery room care of extremely premature infants, including accurate modes to deliver and measure tidal volume and pressure. The best strategy for respiratory support will depend on the development stage and injury status (RDS, infection, hypoplasia, and other lung disease) of individual infants. Infants less frequently develop BPD if they are not intubated during their NICU course.<sup>32</sup>

Postnatal infections increase the risk of developing BPD.<sup>33</sup> Infants who have late-onset sepsis have a longer duration of mechanical ventilation and are more likely to develop BPD.<sup>33</sup> Decreasing infection, the numbers of days of ventilation and ventilator-associated infection may decrease rates of BPD.

Multiple exposures and interventions initiated soon after delivery have targeted BPD prevention. Vitamin A decreased the in-hospital BPD rates,<sup>34</sup> but no differences were observed in subsequent respiratory hospitalizations, oxygen use, or neurodevelopmental outcome at 18-22 months of age.<sup>35</sup> Caffeine used for apnea of prematurity or before extubation (median age of 3 days at initiation) was associated with decreased BPD,<sup>36</sup> and improved death or disability at 18-21 months of age.<sup>37</sup> At 5 years of age,<sup>38</sup> neonatal caffeine administration was no longer associated with an improved rate of survival without disability. At age 11, neonatal caffeine was associated with a reduced risk of motor impairment.<sup>39</sup> Con-

versely, intratracheal recombinant CuZn superoxide dismutase had no effect on the BPD rate, but there was less respiratory medication use, and fewer emergency room visits and hospitalizations up to 1 year of age.<sup>40</sup> High-frequency oscillatory ventilation compared with conventional ventilation does not decrease the rate of BPD or show other short-term benefits, but pulmonary function testing measured at 11-14 years of age was better in the oscillator group compared with those treated with conventional ventilation.<sup>41,42</sup> Finally, continuous positive airway pressure versus intubation and surfactant did not change in-hospital differences in BPD or death,<sup>43</sup> but there was less clinical lung disease at 2 years of age in those treated with continuous positive airway pressure.<sup>44</sup>

Recent data from the PROP multicenter study revealed that in those born at <29 weeks gestational age, perinatal factors present at birth predicted respiratory morbidity at 1 year.<sup>19</sup> We continue to learn from these difficult but critical clinical studies in this fragile patient population. Effective methods of non-invasive respiratory support and standardized approaches to ventilation need further development. Creative analytic statistical approaches such as network meta-analysis can assist in comparing various therapies even when interventions are slightly different.<sup>45</sup> Use of less invasive surfactant administration was associated with the lowest likelihood of death or BPD at 36 weeks PMA.<sup>45</sup> Less invasive surfactant administration provides surfactant directly into the trachea for infants on continuous positive airway pressure without the need for an endotracheal tube to remain in place. In this manner, invasive mechanical ventilation is avoided.

Fluid targets evaluated in the 1970s may not be appropriate today. The infants at risk for BPD today are much smaller and more immature than the infants who developed BPD when original fluid targets were instituted into practice for NICU patients. Further, skin integrity in the very immature infants at risk for BPD is much different than those infants from the 1970s. Multiple questions remain on how sodium supplementation should be handled. What parenteral and enteral nutritional support is best? How can breast milk be best fortified? Do qualitative differences in breast milk affect outcomes? In the PROP first year outcome data, breastfeeding at discharge was independently associated with less later respiratory morbidity.<sup>19</sup> How does general NICU care and practice affect outcomes? It may be of interest for the PROP consortium to examine intercenter differences in outcomes to guide further, detailed examination of these practices by center in this current cohort of 835 babies born at <29 weeks of gestation. There are various care bundles and practices such as clustering care, skin care, and stress reduction that need to be evaluated critically.

The role of the patent ductus arteriosus (PDA) in the development of BPD remains unclear. Although preclinical studies support a link between patency of the ductus arteriosus and the development of BPD, direct evidence from human studies has been difficult to find. In cohort clinical epidemiologic studies, a PDA has consistently been associated with the development of BPD.<sup>46</sup> The absence of an accepted echocardiographic definition that categorizes PDA severity by the magnitude of the left-to-right shunt continues to impede

our understanding of the role of the PDA in BPD. Unfortunately, most randomized controlled trials that have tried to evaluate whether it is better to close the PDA pharmacologically (with indomethacin or ibuprofen) or leave it alone have enrolled patients based on whether the PDA was present or absent, without considering the magnitude of the shunt.<sup>47</sup> In addition, most of the infants in the “no treatment” arm of these studies either were “crossed over” to the “treatment” arm within the first 3-5 days or closed their PDA spontaneously before the end of the first week—making it impossible to determine the relationship between BPD and prolonged exposure to a moderate/large PDA shunt. Also, the previously described PDA randomized controlled trials were all performed before 2000. More recent quality improvement studies have raised concern that delaying the treatment of a moderate/large PDA beyond the first week increases the incidence of BPD and BPD/death.<sup>48,49</sup> It is also noteworthy that centers in the NICHD Neonatal Network that regularly use prophylactic indomethacin (as part of their admission care given within 24 hours of birth) have a significantly lower rate of PDA, BPD, and BPD or death than centers that never use prophylactic indomethacin and only treat the PDA later in the neonatal hospitalization.<sup>50</sup> Future randomized controlled trials that examine the difference between early PDA treatment and either no treatment or rescue treatment beyond 8-10 days will add important information about the effects of timing of treatment and prolonged PDA exposure on BPD. Risks and benefits of treatment including safety need to be assessed in such trials.

Steroids have long been used to prevent or treat BPD. Postnatal dexamethasone can improve lung function and weaning from the ventilator.<sup>51,52</sup> However, dexamethasone administration may increase cerebral palsy rates.<sup>53</sup> Research continues to identify safer postnatal treatment strategies with corticosteroids.<sup>54</sup> A Cochrane Review demonstrates that, if steroids are given after 7 days of age, rates of BPD decrease in the absence of increased neurodevelopmental impairment.<sup>52</sup> Recent trials demonstrate some benefit with postnatal systemic hydrocortisone therapy,<sup>55</sup> aerosolized budesonide,<sup>56</sup> or instilled budesonide mixed with surfactant to decrease BPD.<sup>57</sup> We also need to derive pathophysiologic/mechanistic data underlying neonatal lung injury and abnormal development from laboratory-based studies, so we can develop new clinical interventions. For example, preclinical studies of mesenchymal stromal cells (MSCs) show promise in animal models<sup>58</sup> and have led to a phase I trial conducted in 9 infants.<sup>59,60</sup> Although the time is ripe for well-conducted early phase clinical trials, much more needs to be learned about the mechanism of action of MSC and other potential cell-based therapies. Contrary to the original theory that MSCs engraft and repopulate the damaged lung, evidence suggests that these cells act via a paracrine mechanism.<sup>61</sup> For example, MSC-free derived conditioned media protects type II alveolar epithelial cells, accelerates wound healing of type II alveolar epithelial cells, and preserves the rat lung microvascular endothelium from oxygen injury.<sup>61</sup> This unanticipated mechanism highlights that multiple therapeutic avenues exist to treat and/or prevent BPD—stem cells, or the products released by stem cells.

## Management and Treatment of Established BPD

The clinical management of established BPD has evolved empirically without a strong evidence base. A multidisciplinary approach for severe BPD with the involvement of subspecialists in the NICU, including neonatology, pulmonology, cardiology, otolaryngology, gastroenterology, infectious disease, nutrition, clinical pharmacy, and social work/case management individualized for each patient, may improve outcome.<sup>23</sup> The importance of continuity and team communication was emphasized for these high-risk infants.

Ventilation and respiratory management strategies for infants with established BPD have weak evidence to support current practices. A better understanding of BPD phenotypes is needed because BPD is such a heterogeneous group of patients. Precursors to BPD include parenchymal lung disease, vascular injury with pulmonary hypertension, airway injury or control of breathing issues necessitating prolonged respiratory support, and aspiration, and may require different care strategies. Other variables that influence management decisions include the types of ventilator and respiratory equipment used, pressure and tidal volume approaches, and ventilator rates. Optimal oxygen saturation targeting has been studied at various time points in the NICU. Studies by Askie et al (BOOST)<sup>62</sup> and Phelps (STOP-ROP)<sup>63</sup> showed that higher oxygen saturation targets begun at an average of 32 and 35 weeks PMA are associated with worse pulmonary outcomes as measured by duration of oxygen exposure at 38 weeks PMA and 3 months PMA. More recent oxygen saturation target trials<sup>64-69</sup> have been summarized in a current report from the American Academy of Pediatrics.<sup>70</sup> This report concluded that a targeted saturation range of 90%-95% may be safer than 85%-89%, but the ideal saturation range for extremely low birth weight infants remains unclear. The results of a neonatal oxygenation prospective meta-analysis (NEOPROM) are pending.<sup>71</sup> Nutrition strategies for the BPD population are generally aimed at higher calories with fluid limitation. None of these practices have been studied rigorously in large populations. Future analysis of individual genomics may help to guide personalized nutrition choices for each baby.

Diuretics, bronchodilators, and corticosteroids (inhaled and systemic) are frequently used in infants with established BPD.<sup>23</sup> Data from the 835 infants recruited from 5 centers and 13 clinical sites for the PROP dataset demonstrate that medication usage varies widely. There is a lack of clear diagnostic definitions for pulmonary hypertension in BPD. Whether pulmonary hypertension is a marker for more severe BPD or directly contributes to worse outcomes remains unclear.<sup>72</sup> When detected, pulmonary hypertension seems to increase the risk of death in infants with BPD,<sup>73</sup> and further studies are needed to identify these at-risk infants earlier. Biomarkers and echocardiographic criteria are gaps in knowledge. For infants with suspected or established pulmonary hypertension complicating BPD,<sup>74</sup> additional medications such as nitric oxide, sildenafil, bosentan, and treprostinil are used clinically but not well-studied. Prospective randomized trials are needed to in-

vestigate the benefit of these pulmonary vasodilators are needed.<sup>75</sup> In addition to studying treatment and management, a better understanding of the pathophysiology underlying BPD-associated pulmonary hypertension is needed.

Interdisciplinary care for infants with severe BPD was recently reviewed.<sup>23</sup> Even though there have been significant advances in neonatal care over the past several decades, many infants are at high risk and go on to develop BPD. Abman et al highlight the need for basic and translational research to understand BPD pathogenesis as well as testing clinical interventions at multiple sites.<sup>23</sup> Epidemiology and outcomes research are needed to develop better care strategies for BPD, particularly for severe BPD.

## Chronic and Home Care for BPD

Home-based care is optimal when there is clear communication with families regarding the disease process as well as the medical plan for management. In addition, the home environment, including the presence of siblings, cigarette smoking, pets, heat sources, and other factors, influence the overall health of the infant once discharged home and likely affect the rates of chronic pulmonary morbidity. Maternal smoking was associated independently with more respiratory morbidity in the first year in the current PROP cohort,<sup>19</sup> and should be a target area for NICU personnel to work on with families. Discharge preparation involves caregiver training in all aspects of care. Identification of the signs of respiratory distress or illness, medication use, equipment use, oxygen management, and ventilator or tracheostomy care are ideally demonstrated by the primary caregivers before discharge.

Follow-up of the high-risk BPD population involves the active collaboration of general pediatricians as well as many subspecialists. General pediatric issues, such as vaccination, anticipatory guidance, and well-child care, have not been studied in such populations. Outpatient clinic follow-up and the frequency of these visits for primary care and subspecialist visits are not well-delineated. Further, specific testing such as exercise stress tests, echocardiogram, lung function testing, and various other monitoring have not been well-studied in this population.

## Revisiting a BPD Definition

Current definitions of BPD include the use of supplemental oxygen treatment or oxygen plus respiratory support at 36 weeks PMA to define BPD for very low birthweight infants. A single “yes/no” definition may be impractical; BPD needs to be categorized by severity for multiple purposes. These purposes include, but are not limited to, epidemiology, as an outcome for clinical trials, and as a predictor for longer term outcomes. Some interventions with a higher risk-benefit profile could be reserved for those babies predicted to have more severe BPD or more severe respiratory morbidity after discharge. Detailed assessments of oxygen or ventilator support histories of patients are impractical for epidemiology, but may be better at predicting long-term respiratory outcome. Further, new treatment strategies using very low nasal cannula flow rates with 100% oxygen or high flow with room air (21% oxygen) render some infants unclassifiable by previously published standard definitions. The definitions also do not include infants progressing toward a 36-week definition of BPD who die of their respiratory failure before 36 weeks, the most severe form of lethal BPD; these babies do not get a “BPD” classification of any kind yet should be “counted” operationally when answering some clinical research questions.

The participants of the workshop have proposed a new skeleton definition of BPD (**Table I**) to stimulate the development and validation of new BPD definitions. The proposed scheme for a revised definition considers newer modes of non-invasive ventilation that were not included in the previous definitions. We propose using new terms of grades I, II, and III. Mild, moderate, and severe may be subjective and interpreted differently by individual clinicians. Grade III would refer to the most severe form of BPD. Continuation of the 36-week PMA timepoint is suggested because most infants remain in the hospital at this timepoint, which makes ascertainment of a diagnosis of BPD possible for many patients.

Given the changing NICU population over the past 50 years since the first description put forth by Northway et al,<sup>1</sup> BPD as first described now affects a radically different population of extremely premature infants. Some larger infants still develop BPD, generally in association with other abnormalities. Thus, the population of infants that develops BPD in the current era is heterogeneous. There is clearly a need for better

**Table I.** Suggested refinements to the definition of BPD

A premature infant (<32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires 1 of the following  $\text{FiO}_2$  ranges/oxygen levels/ $\text{O}_2$  concentrations for  $\geq 3$  consecutive days to maintain arterial oxygen saturation in the 90%-95% range.

Grades	Invasive IPPV*	N-CPAP, NIPPV, or nasal cannula $\geq 3$ L/min	Nasal cannula flow of 1-<3 L/min	Hood $\text{O}_2$	Nasal cannula flow of <1 L/min
I	—	21	22-29	22-29	22-70
II	21	22-29	$\geq 30$	$\geq 30$	$>70$
III	>21	$\geq 30$			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

\*Excluding infants ventilated for primary airway disease or central respiratory control conditions.

Values are percents.

CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; N-CPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation.

phenotypic and endotypic characterization of infants with BPD. In addition, there is a need for a definition that is more granular than a dichotomous outcome, both for observational studies and interventional trials that seek to better understand this heterogeneous disease. The scheme for a proposed definition for premature infants considers newer modes of noninvasive ventilation (**Table I**), which are problematic when applying the currently available definitions.

## Conclusions

BPD is a complex and multifactorial disease that remains poorly understood and inadequately defined, despite much scholarly work in both areas. Many gaps and opportunities for research were identified (**Table II**). The workshop participants observed that at present there is lack of information on the natural history of BPD. They also noted that there is a need

**Table II. Challenges and opportunities for BPD research**

### General gaps

- Define parenchymal lung disease—evaluate the role of radiological methods in improving the diagnosis.
- Pulmonary vascular disease should be incorporated into the classification and/or severity of BPD.
- New techniques to identify primary airway disease in the BPD population.
- Better define the BPD phenotype of SGA/IUGR infants
- Future studies to validate the definitions including newer respiratory support modes and practices of room air flow and CPAP, low-flow nasal cannula, high-flow nasal cannula, and other emerging technologies and devices for delivery of respiratory support.
- A better understanding of maternal diet and placental function, exposure to toxins, and smoking.
- Human lung samples from premature infant autopsy specimens with and without BPD to really improve our understanding of the evolution of this disease.

### Delivery room intervention gaps

- Challenges with antenatal consent.
- Delayed cord clamping versus cord milking incorporating mode of delivery with BPD as a secondary outcome.
- Noninvasive surfactant administration techniques.
- Initial recruitment of lung volumes—sustained inflation.
- Respiratory function and  $\text{CO}_2$  monitoring in the delivery room, specifically devices and utility.
- Pressure and tidal volume measurements and delivery.
- CPAP delivery devices relative to delivery room and NICU geography.

### Gaps for NICU management from birth to 36 weeks postconceptional age

- Need for pharmacokinetic, phase 1 and phase 2 studies before larger medication trials.
- Optimization of nutritional interventions and human milk fortification.
- Fluid intake and targets for optimum fluid and electrolyte (including sodium) balance.
- Evaluate the role of early, prolonged PDA exposure and drugs used to treat the PDA.
- Defining postnatal window for susceptibility to BPD.
- Invasive and noninvasive ventilation strategies.
- Potential novel therapies for BPD.
- Antioxidant therapies.
- Growth factor therapies (insulin-like growth factor, proangiogenic factors).
- Immunomodulatory agents.
- Anti-inflammatory and selective anti-cytokine therapies.
- Mesenchymal stem cells and cell-based therapies.
- Identification of populations of infants progressing toward BPD for clinical trials.
- Evaluate variance in practice to improve BPD care.
- Better understanding of why /SGA infants have high rates of BPD.
- Microbiome research in the context of BPD
- Urea plasma as a contributor to BPD.
- Proteomics as well as other “omics.”
- Candidate drugs and management strategies for clinical trials.

### Follow-up gaps

- What regular pediatric care should look like?
  - Vaccinations.
- When?
  - Every 6 months at least through 3 years.
- Which babies? (Needs to be informed by natural history.)
  - All those <25 weeks gestational age.
  - All those going home on oxygen.
  - Case-by-case basis.
- Optimal subspecialty care strategies.
  - Respiratory management including recurrent wheezing and asthma.
  - Better understanding of function and development.
  - Nutrition.
  - Home environment.
    - Pulmonologists.
    - Respiratory therapists.
    - Neurodevelopmental specialists.
    - Social workers—help with adherence to medications.
    - If needed: cardiologists (for those with pulmonary hypertension) ENTs, GI, nutritionists.
    - Pharmacists—even if not meeting with family, at least reviewing prescriptions.
    - Nurse practitioner or case manager to track all of this, track the patients, schedule appointments, etc.

CPAP, Continuous positive airway pressure; ENT, ear, nose, and throat specialist; GI, gastroenterology; SGA, small for gestational age; IUGR, intrauterine growth restriction.

for intervention trials to prevent and to treat BPD. Studies are also needed to provide evidence-based guidelines to assist clinicians in caring for both the newborn infant at risk of developing BPD and those with established BPD. Critical areas in need of urgent study include postnatal management of the smallest infants to prevent BPD or to decrease the severity of BPD; respiratory and medication management of established BPD; and diagnosis, management, and treatment of BPD-associated pulmonary hypertension, which has very high mortality and morbidity. In addition, it is important to obtain more information on the short- and long-term outcomes of BPD, including the study of the complex association with neurodevelopmental impairment. Increasing the evidence base to guide clinical practice is necessary to improve respiratory and other outcomes in premature infants. ■

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