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Chronic Pulmonary Insufficiency of Prematurity: Developing Optimal Endpoints for Drug Development

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Introduction

Chronic pulmonary insufficiency is the most common morbidity of extremely preterm birth. It is associated with increased resource utilization during the initial hospitalization, as well as short and longer-term respiratory morbidities that drive health care costs and are associated with worse neurodevelopmental outcomes (1).

Chronic pulmonary insufficiency of prematurity (CPIP) refers to respiratory morbidity after preterm birth during the birth hospitalization and through infancy and childhood (Figure 1). It is usually captured during the initial hospitalization using a diagnosis of bronchopulmonary dysplasia (BPD). Despite advances in respiratory management, the incidence of BPD in the smallest neonates continues to rise, (2) and there have been few therapeutic advances over the last 25 years (3). There are many reasons for these ongoing gaps in drug development including difficulties with clinical trial design, a population that is viewed as high risk by regulators and industry, and the need to wait months or even years to establish safety and efficacy. These problems are compounded by definitions of BPD that are applied inconsistently and are not clearly related to long-term outcomes of importance to clinicians and families.

Consideration of CPIP is important because the diagnosis of BPD does not capture all infants with chronic pulmonary insufficiency. The concept of BPD grew out of radiological and pathological examinations of neonates with significant lung injury, and assumes that an oxygen requirement stems from lung damage that is similar between infants, and that different lung insults produce similar effects on the lung. While oxygen dependence is related to injury of the lung parenchyma, it may also be influenced by injury or immaturity of the brain, airways, or pulmonary vasculature. Moreover, an early measure of gas exchange may not reflect the pathophysiology of later problems such as reactive airways disease or susceptibility to viral infections. Optimizing and harmonizing clinical definitions of CPIP, including BPD and later respiratory outcomes, while developing strong surrogate endpoints useful for regulators, industry, clinicians and families would greatly benefit future interventional trials and accelerate the development of new therapies for these high risk and vulnerable patients.

Current Endpoints: Benefits and Limitations for Drug Development

The definition of BPD has evolved substantially over the past 50 years in conjunction with improved survival for extremely low birth weight (ELBW) infants (Table 1). While CPIP exists on a continuum of disease severity over time, BPD is defined as a dichotomous (yes/no) outcome of requirement for supplemental O_2 at an arbitrary 36 week PMA time point. There is not consensus that BPD predicts chronic pulmonary insufficiency or represents the most appropriate definition for clinical trials of drug development (4). A recent systematic review found that many clinical trials did not use a discrete BPD definition (5), a situation complicated by the absence of biomarkers or imaging techniques to characterize or predict BPD.

An additional challenge is that criteria for O_2 use for treatment of upper airway disease or immaturity of respiratory control (e.g. apnea and feeding difficulties) vary between centers and clinicians. For example, in the multicenter Prematurity and Respiratory Outcomes Program (PROP) study, 47% of 765 surviving ELBW infants remained on nasal cannula support at 36 weeks PMA, but with substantial variation in the flow and/or O_2 concentrations used (6). Although an infant receiving 21% O_2 delivered at 4 liters/minute (LPM) by high flow nasal cannula would be classified as 'no BPD' by the Shennan definition, it is not known whether there is less intrinsic lung disease and better long term outcomes than an infant receiving 0.1 LPM of 100% O_2 and classified as ‘severe BPD’.

BPD is a functional description that is not correlated to specific mechanisms but has become shorthand for CPIP in general. A functional description may be useful in clinical trials as a way to capture multiple influences. However, the current 36-week PMA definition of BPD remains an imperfect surrogate to predict chronic pulmonary morbidity in infancy, later childhood and adolescence. For instance, some interventions such as vitamin A significantly reduced the incidence of BPD at 36 weeks PMA, but did not affect long-term respiratory morbidity (7, 8). Other interventions such as high frequency oscillatory ventilation, superoxide dismutase and late surfactant failed to reduce BPD, but improved longer-term respiratory outcomes (9-11). These discrepancies may reflect the range of tissues

that can be injured in premature babies: Vitamin A may support more efficient gas exchange in the short term but have no effect on airways, while other interventions may have their dominant effects on airways or other tissues. BPD may still be a useful as a functional clinical outcome that captures lung function at the time a preterm infant should transition out of the hospital, in the way that functional outcomes such as FEV1 are useful in conditions such as cystic fibrosis.

Goals of definitions: Perspectives of Clinicians, Industry, Regulators and Parents

How should respiratory disease of prematurity be optimally defined for the purposes of drug development? Ideally, a definition would be clinically meaningful and strongly associated with the subsequent development of long-term respiratory morbidities. The definition should be objective, standardized, and incorporate unambiguous, specific guidance about how to factor in the use of O_2 and non-invasive respiratory support. As other morbidities of prematurity (eg, necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage) are measured on a scale, a validated "BPD severity scale" ranging from no morbidity (no O_2, respiratory support, or medications) to severe morbidity would be useful. Definitions should use components that are easily extractable from the health record, and allow for the reliable evaluation of infants transferred to another hospital or discharged before the optimal time of BPD assessment, since these infants are often not appropriately classified (6, 12). Definitions should also incorporate infants that die of progressive lung injury between 7 days of life and 36 weeks PMA, as these infants may gain the most from early/prophylactic treatment approaches.

From the perspective of the pharmaceutical industry, a simple and pragmatic definition will encourage its introduction into routine neonatal clinical practice in all hospitals, not just at university and research based institutions. Regulatory authorities need to assess whether endpoints other than survival measure a meaningful aspect of how a patient feels or functions in daily life. Endpoints should display good inter- and intra-observer agreement and stability over time in individual babies; and have a predictable relationship to mechanisms that are amenable to drug therapy, which will facilitate dose selection and the development of biomarkers.

Industry, trialists, and regulators also need to consider the perspective of parents on what constitutes meaningful outcomes. Composite outcomes such as "death or BPD" can be difficult for

parents to understand, as families do not view these competing outcomes as equivalent (13). Moreover, if an infant survives, a requirement for a nasal cannula at 36 weeks PMA has a very different impact compared to home oxygen or ventilation. Moving beyond the dichotomous BPD outcome to include the long-term consequences of lung injury will measure outcomes that are important to this group.

Proposed endpoints for clinical trials that investigate CPIP

36 week PMA definition of BPD: When compared to term infants, ELBW infants are at higher risk for pulmonary morbidity. Premature infants with BPD have longer initial hospitalizations, increased rates of death and long-term disability, use of respiratory medications, and abnormal pulmonary function during childhood (14). However, other studies have failed to demonstrate significant differences in long-term pulmonary outcomes for infants with and without BPD at 36 weeks PMA (14-16), leading regulators to increasingly view the 36-week endpoint as inadequate for drug approval.

Restricting the diagnosis of BPD to a dichotomous outcome limits information about the disease itself. The definition of BPD at 36 weeks PMA should be expanded to a continuous outcome that incorporates all methods of non-invasive respiratory support and use of respiratory medications (diuretics, bronchodilators, corticosteroids) that can influence the need for supplemental O_2. We propose incorporating a simple respiratory checklist administered at 36 weeks PMA or discharge into the health records of all preterm babies, to allow development of an objective BPD scoring system, particularly for those infants transferred to another hospital or discharged home (Table 2). Endpoints at 36 weeks PMA should also incorporate pulmonary hypertension screening for infants with moderate to severe BPD, which is found in 10-15% of this population and associated with higher mortality and morbidity (17-19). Finally, the 36-week PMA determination is typically made on a single day during the 36^{th} postmenstrual week, despite changing needs for supplemental O_2 because of immaturity in control of breathing, feeding patterns, and airway protection inherent to this time period. This variability in timing likely contributes to the poor long-term predictive value of a 36 weeks PMA diagnosis. We recommend extending the assessment of oxygen dependency to maintain the oxygen saturation in the normal range (90-95%), and to include at least 3 consecutive days of the 36^{th} postmenstrual week.

40 weeks PMA: As immature respiratory control and feeding difficulties often resolve by term equivalent, targeting a 40 week PMA endpoint may improve upon the pitfalls of the 36 week endpoint and better identify those infants with persistent airway and/or parenchymal disease. Although some infants will already be discharged, the PROP cohort found that 41% of survivors (315/765) were still in the hospital at 40 weeks PMA (6). A child could be imputed as "No BPD" at 40 weeks PMA or the time of discharge if off all respiratory support (including non-invasive methods) for a period of time (e.g. 7 days). The result would be an alternative definition at 40 weeks PMA or discharge that is dichotomous (NO BPD if in RA with no support, YES BPD if receiving any form of support) but also continuous by assigning a score based on levels of respiratory support. A numeric scale that incorporates inspired O_2 concentration, flow rate and medication use would have the advantage of being a statistically more powerful outcome than a simple dichotomous outcome. For instance, data from the Canadian Neonatal Network show that a combined outcome of O_2 or respiratory support (oxygen, CPAP, or ventilator use) at 40 weeks PMA was a superior predictor of serious respiratory morbidity at 18-21 months corrected gestational age (CGA) (20). However, this time point must still be validated in multiple international cohorts.

1 year CGA: Premature infants more frequently have pulmonary morbidity at school age and beyond, including asthma, repeated pulmonary infections, exercise intolerance, and lung function abnormalities (14, 16). These are important outcomes, but impractical endpoints for most neonatal interventional trials. In addition, these long-term respiratory morbidities may occur regardless of the development of BPD, suggesting that mechanisms for longer-term pulmonary morbidity may differ from those causing O_2 dependency at 36 weeks PMA (21). One small study suggested that pulmonary function testing at one year CGA predicted respiratory symptoms at five years of age while a diagnosis of BPD at 36 weeks did not (22). Unfortunately, lung function assessments at one year CGA use complex equipment not available at most centers and sedation of the infant, leading most parents to refuse consent (23).

Outcomes such as the need for re-hospitalization, home O_2 therapy, and frequent visits to a health care provider or the emergency department in the first years of life have not been systematically reported in most studies, although this is beginning to change (24, 25). The use of respiratory medications (e.g.

bronchodilators, inhaled/systemic steroids, leukotriene inhibitors) to treat respiratory symptoms or illnesses during the first year of life also suggests the presence of chronic respiratory morbidity, but is limited by the absence of evidence of efficacy, clear standards for treatment, and marked center-to-center variability.

At one year CGA, a four-week respiratory diary card completed by parents captured the extent of coughing, wheezing and respiratory medications use and was highly predictive of two-year respiratory outcomes (15). This study did not find that re-hospitalization was a significant predictor of longer-term respiratory dysfunction. However, the total number and duration of hospital re-admissions was related to the severity of BPD and is a clinically meaningful outcome for families. The biggest problem with using a primary one year outcome measure is the impact of confounding variables such as environmental factors such as smoking in the home, medication compliance (including any immunoprophylaxis), and respiratory syncytial virus (RSV) and other viral infections. Furthermore, while rates of follow-up are 97% in the UK and Australia, improved rates of follow-up in other countries such as the US would need to be achieved.

Other Outcome Considerations

Premature infants who have continuing pulmonary insufficiency at the time of hospital discharge present a significant challenge for the parents, family, and primary care providers. Common problems for these infants are marginal nipple feeding; the need for partial or complete gavage feeding; fussiness, irritability and inconsolability; and the need for multiple medications and medical visits. Outcomes such as growth, sleep patterns, behavioral and neurodevelopmental issues, and parental stress are also very important (13). An objective Quality of Life (QOL) scale is needed for this age group to obtain input from the parent as well as timely observations regarding their infant. The PedsQL™ Pediatric Quality of Life Inventory Infant Scales is one such instrument for children ages 2-12 years of age (www.pedsql.org/index.html). There would be a role for developing smart mobile tools to provide an easily accessible portal for parents to fill out serial QOL assessments.

Identification of Severe or Early Lethal CPIP

The population of ELBW infants most in need of innovative therapies may be those who die of "early, lethal BPD" before a diagnosis of BPD can be formally made. The cause of death for these infants is often imprecisely assigned. When the NICHD Neonatal Research Network (NRN) examined deaths over 19 years, infants died of “RDS” well past the first week of life, and died of "BPD" prior to 36 weeks PMA.(26) In the recent PROP cohort, 63/835 ELBW infants died prior to 36 weeks PMA (6). Of the 35 infants who died after two weeks of age, 25 (71%) were retrospectively adjudicated to have had chronic respiratory failure as a primary cause of death. Chronicity was arbitrarily assessed by the respiratory status within seven days of death, with many of these infants having been assigned other causes of death. Thus, about 3% of the entire cohort had "early lethal BPD".

Clinical trials often report the combined outcome of death or BPD because death prior to 36 weeks PMA is a competing adverse outcome. However, neither epidemiologic nor trial reports independently identify deaths due to severe respiratory failure prior to 36 weeks PMA. These deaths are often associated with elements of a BPD phenotype, and some of these deaths may be due to complications (e.g. sepsis) that may have occurred secondary to the care needed to support the respiratory failure, such as the prolonged need for vascular access and respiratory support, nutritional deficits and prolonged antibiotic exposure.

The concept of severe CPIP or BPD should also evolve to better capture those infants who survive to 36 or 40 weeks PMA and have severe respiratory failure needing aggressive treatment. There is a need for valid predictors for the severe form of CPIP that can be applied soon after birth and within the first several weeks of life, as these infants should be specifically targeted for trials of innovative therapies. A modified NICHD BPD Calculator may be a good option for such a predictive instrument (27). For example, continued need for mechanical ventilation at day seven is a strong indicator for increased BPD risk, yet this likely indicates a need for even earlier predictors (e.g., antenatal factors, need for resuscitation).

Perinatal Risk Factors: Implications for Preventive Studies

Many of the factors and co-morbidities associated with CPIP can be used to identify populations at highest risk. Antenatal factors such as intrauterine growth restriction (IUGR), maternal hypertension, maternal smoking, and male gender are now appreciated to be key risk factors and highly predictive of chronic respiratory morbidity (24, 28). Postnatal events that increase the risk of BPD include severe respiratory failure, air leak, early pulmonary hypertension, systemic and pulmonary infections and the prolonged presence of a patent ductus arteriosus.

Intrauterine Growth Restriction: One of the strongest factors reflecting the impact of fetal events in the pathogenesis of BPD is the presence of IUGR (29, 30). In one large study of preterm infants $\leq$ 28 weeks gestation, birth weight z-scores indicative of IUGR were more strongly linked with increased risk for BPD than numerous other prenatal, placental and postnatal factors (29). Furthermore, IUGR is an independent risk factor for late respiratory morbidities and abnormal lung function at school age (e.g. abnormal airway function, decreased lung surface area) (31, 32).

Placental abnormalities: Hypertensive disorders of pregnancy such as pre-eclampsia have been strongly associated with the development of BPD after preterm birth, even after accounting for IUGR (33). Experimental models that alter placental function and structure to create severe IUGR impair fetal lung airspace and vascular growth in the late gestation fetus, which may persist throughout postnatal life (34). In preterm infants with IUGR, histologic placental abnormalities of "maternal under-perfusion" are strongly linked with BPD and BPD-associated pulmonary hypertension. Cord blood biomarkers for assessing BPD risk may include circulating fetal proteins such as vascular endothelial growth factor (VEGF) and soluble fms-like tyrosine kinase-1 (sFlt-1; also known as soluble VEGF receptor-1) (35).

Maternal smoking: Maternal smoking is a known risk factor for impaired lung function, wheezing and asthma in children at 4 – 12 years of age (28, 36) and likely contributes to CPIP outcomes (24, 37). Possible mechanisms underlying the harmful effects of maternal smoking on fetal lung development could be dysregulated cytokine production and oxidative stress, or direct effects of nicotine on lung receptors resulting in altered lung development and impaired lung function at birth (38). More recent research has suggested an interaction of *in utero* and early life smoke exposure with upregulation of

asthma susceptibility genes (39) and new evidence suggests the effects of maternal smoking can be modified by agents such as Vitamin C (40).

Inflammation and infection: Preterm birth is frequently associated with fetal exposure to inflammation/infection as diagnosed by histopathology (e.g. chorioamnionitis, funisitis), culture, or increased concentrations of pro-inflammatory cytokines in amniotic fluid or cord blood (41). Chorioamnionitis rarely results in invasive infection, but indicators of lung inflammation prior to birth are frequently found (42). These antenatal exposures are associated with lung abnormalities that range from severe diffuse pneumonia (indistinguishable from severe RDS) to mature lungs for gestational age with lower risk for BPD. Although fetal modulations of immune and inflammatory responses can contribute to postnatal lung injury and the development of BPD, the exact mechanisms are poorly understood (43). Postnatally, lung inflammation can be triggered by exposure to systemic infection, high O_2 concentrations, positive pressure ventilation, and/or a patent ductus arteriosus. Increased concentrations of inflammatory mediators could contribute to bronchoconstriction, vasoconstriction and increased vascular permeability characteristic of the lungs of these infants and might also be responsible for the decreased alveolarization seen in infants dying with BPD (44).

Pulmonary vascular disease: Disruption of pulmonary angiogenesis due to antenatal factors such as chorioamnionitis, pre-eclampsia, maternal smoking, and postnatal injury can cause pulmonary vascular disease that leads to pulmonary hypertension (PH) and impaired distal lung growth (19). Echocardiographic findings of pulmonary vascular disease shortly after preterm birth are strongly associated with the development and severity of BPD and PH at 36 weeks PMA, as well as late respiratory complications including respiratory exacerbations, hospitalizations and the need for asthma medications (45). Echocardiographic evidence of early PH may be an excellent predictor of severe BPD and an early predictive biomarker for enrolling the highest risk infants into clinical intervention trials.

Early respiratory failure: Severe RDS and the need for high inspired O_2 concentrations and prolonged ventilatory support are clearly associated with an increased incidence of BPD. The ongoing need for respiratory support at day seven improves the predictive accuracy for BPD, with rates approaching 65% (27, 46, 47). O_2 targeting trials have shown increased pulmonary morbidity in infants

maintained within higher O_2 target ranges, suggesting that higher inspired O_2 may produce worse pulmonary outcomes. A recent secondary analysis of the TOLSURF trial showed a strong association between cumulative O_2 exposure during the first 14 days and a higher incidence of BPD at 36 weeks PMA (48). Thus, an analysis of cumulative inspired O_2 concentrations (area under the curve) may permit the early prediction of BPD or other forms of CPIP with a high degree of specificity and sensitivity (48).

Research agenda

The research agenda for drug development needs to sharpen its focus on rigorous data collection combined with a mechanistic approach appropriate for clinical scientists.

1. Identification of subgroups of CPIP: Rigorous studies are needed to determine that specific risk subgroups exist and can be reliably identified. Hypotheses about subgroups can be generated from epidemiological data (including cohorts that are characterized with modern methods, such as –omics) or from mechanistic data (usually derived from *in vitro* or animal models). One set of hypotheses could be based on the risk factors described above: for example, IUGR could be associated with different pathways and manifestations of CPIP when compared to perinatal inflammation. These studies should pay attention to genetic factors that may contribute to severe CPIP. Subgroups could be defined according to *a priori* criteria, or could be identified from linking clinically important outcomes to phenotypic or –omic profiles. Proposed subgroups need to be confirmed using validation cohorts. Biomarker inquiries should cover the pre-analytic and analytic characterization of proposed biomarkers and quantification of the variability of that biomarker observed in the target population.

2. Identification of respiratory outcomes: Specific respiratory outcomes at the proposed time points need to be reliably ascertained as clinically relevant or have strong associations with functionally relevant outcomes. International data sets and registries should be used to determine covariates that contribute to the progression or resolution of chronic pulmonary insufficiency. New techniques should be developed and studied to better standardize pulmonary assessment, such as imaging techniques that measure alveolar numbers and sizes (26), or noninvasive measurements of exhaled gases.

3. Relationship between subgroups and outcomes: Studies need to determine whether specific subgroups are strongly associated with clinically significant outcomes. Newer methodologies such as phenotype-wide association study (PheWAS), structural equation modeling, or latent variable analysis should be considered. Characterization needs to include quantification of the variation in the strength of the association within and across clinical settings, as well as an estimate of the magnitude of the association.

4. Impact of a drug or other intervention on an outcome among specific subgroups: This involves testing whether members of a subgroup are more likely to have a beneficial outcome, or less likely to have an adverse outcome, in response to a drug across its therapeutic range.

We suggest that these investigations will require a staged program linking subgroup characterization to outcomes and drug response. The stages could be done in parallel in carefully designed studies. The use of BPD as an outcome for drug development in the absence of these steps may be a historic necessity but it has led to a lack of clarity and may have led to inappropriate rejection of promising drugs. Future work will benefit from the steps we outline.

Conclusions

A single definition of CPIP is unlikely to address all the needs of trialists, drug developers, parents and regulators for meaningful and valid endpoints. For some purposes, refining the existing 36-week PMA definition of BPD to better predict long-term pulmonary insufficiency would retain the advantages of assigning a diagnosis prior to discharge. There is also a need to better understand the impact of severe lung disease that leads to early mortality prior to the designation of BPD at 36 weeks; this has been an overlooked population that needs study and warrants clinical trial work. A 40-week PMA definition would be anticipated to reduce the 'noise' by eliminating infants with minimal disease, but would need further validation for its predictive value. A one-year CGA outcome capturing features of chronic respiratory morbidity remains essential to regulators and families as a clinical meaningful outcome, but needs validation, comprehensive follow-up and the ability to control for post-discharge environmental factors. Finally, identification of subpopulations of infants at highest risk, or with

pathophysiology that may benefit from a particular therapy, is needed to allow clinical trials to function optimally and conclude with clear answers.

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