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REVIEW

Management of hypoxemic respiratory failure and pulmonary hypertension in preterm infants

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While diagnoses of hypoxemic respiratory failure (HRF) and pulmonary hypertension (PH) in preterm infants may be based on criteria similar to those in term infants, management approaches often differ. In preterm infants, HRF can be classified as 'early' or 'late' based on an arbitrary threshold of 28 postnatal days. Among preterm infants with late HRF, the pulmonary vascular abnormalities associated with bronchopulmonary dysplasia (BPD) represent a therapeutic challenge for clinicians. Surfactant, inhaled nitric oxide (iNO), sildenafil, prostacyclin and endothelin receptor blockers have been used to manage infants with both early and late HRF. However, evidence is lacking for most therapies currently in use. Chronic oral sildenafil therapy for BPD-associated PH has demonstrated some preliminary efficacy. A favorable response to iNO has been documented in some preterm infants with early PH following premature prolonged rupture of membranes and oligohydramnios. Management is complicated by a lack of clear demarcation between interventions designed to manage respiratory distress syndrome, prevent BPD and treat HRF. Heterogeneity in clinical phenotype, pathobiology and genomic underpinnings of BPD pose challenges for evidence-based management recommendations. Greater insight into the spectrum of disease phenotypes represented by BPD can optimize existing therapies and promote development of new treatments. In addition, better understanding of an individual's phenotype, genotype and biomarkers may suggest targeted personalized interventions. Initiatives such as the Prematurity and Respiratory Outcomes Program provide a framework to address these challenges using genetic, environmental, physiological and clinical data as well as large repositories of patient samples.

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INTRODUCTION

Advances in neonatology in recent years have improved the outlook for premature infants with hypoxemic respiratory failure (HRF) and pulmonary hypertension (PH). Treatment strategies continue to evolve with increasing clinical experience and greater understanding of the underlying nature of HRF and PH.[1] Similar to term infants, diagnoses of HRF and PH are usually based on clinical observations of altered gas exchange with reduced oxygenation and echocardiographic evidence of increased pulmonary vascular resistance and exclusion of cardiac and other non-pulmonary causes. Measurement of arterial oxygen tension (PaO_2) and/or peripheral oxygen saturation (SpO_2) in combination with mean airway pressure and inspired oxygen concentration can be used to derive quantitative measures, such as oxygenation index and oxygen saturation index of HRF.[2] Simplified 'slide rule' methods for determining shunt and right shift (reduced ventilation/perfusion ratio (V_A/Q)) of inspired oxygen pressure (PiO_2) versus SpO_2 have also been described, allowing wider clinical application.[3] However, the diagnosis of HRF and PH in preterm infants is complicated by the lack of precise criteria and well-established thresholds for a given gestational age (GA) and postnatal age. An arbitrary threshold of 28 postnatal days is sometimes used to classify HRF/PH as 'early' or 'late'. Management continues to be challenged by imprecise definitions of HRF/PH in the preterm population and a lack of clear demarcation between interventions designed to treat early HRF with or without accompanying respiratory distress syndrome (RDS) and those designed to prevent bronchopulmonary dysplasia (BPD) and associated late PH.

This article discusses knowledge gaps and challenges surrounding the management of HRF, PH and BPD in preterm neonates and infants. It is part of a series summarizing expert presentations and discussions from a roundtable that focused on HRF in neonates (see the Introduction to this issue).

EARLY HRF

Increased pulmonary arterial pressures can manifest in preterm infants with significant lung pathology, including RDS,[4,5] BPD,[6–8] and following conditions, such as premature prolonged rupture of membranes (PPROM) and oligohydramnios.[9–12] PH has also been seen following exposure to some medications (e.g., maternal nonsteroidal anti-inflammatory drugs, neonatal ibuprofen).

Conceptually, management strategies for HRF in premature neonates aim to: (1) resolve the underlying medical condition (e.g., pneumonia, RDS); (2) address the fundamental pathophysiology (e.g., improve V_A/Q mismatch for HRF and induce pulmonary vasodilation and prevent or reverse vascular remodeling for PH); and/or (3) circumvent the problem by reducing hypoxemia despite persistent pathology (e.g., increase fraction of inspired oxygen (FiO_2)). In early HRF, interventions typically focus on preventing lung injury and improving V_A/Q matching by optimizing lung inflation.

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Respiratory support and surfactant replacement are cornerstones in the management of RDS. Respiratory support strategies include continuous positive airway pressure (CPAP), high-flow, humidified support via nasal cannula and invasive mechanical ventilation. There are limited data suggesting volume-targeted ventilation may be more suitable than pressure-limited ventilation for preterm neonates;[13,14] however, there is no compelling evidence favoring high-frequency oscillatory ventilation over conventional ventilation.[15]

Surfactant therapy has been well studied in numerous large randomized trials in premature neonates.[16,17] The 'INSURE' method, which involves intubation–surfactant–extubation to CPAP, reduces the need for mechanical ventilation.[18] CPAP is also an acceptable alternative to surfactant administration in preterm infants with RDS.[19] Large trials have demonstrated the benefit of early stabilization on CPAP with the selective use of surfactant therapy.[20,21] In fact, guidance from the American Academy of Pediatrics strongly recommends consideration of CPAP immediately after birth with selective surfactant use as an alternative to routine intubation and prophylactic surfactant administration.[19]

Maintenance of optimal lung volume remains important regardless of ventilation modality and underlying pulmonary pathology. Strategies to achieve optimal lung inflation include use of positive end-expiratory pressure or CPAP, high-frequency ventilation and administration of surfactant. Some centers target an arterial CO_2 partial pressure ($PaCO_2$) between 45 and 55 mm Hg in the first week of life. Limited permissive hypercapnia ($PaCO_2$ >52 mm Hg) may have some benefit over routine adult ventilation targets ($PaCO_2$ <48 mm Hg) in extremely preterm infants.[22] In addition, a liberal oxygen saturation target (SpO_2, 91% to 95%) has been associated with lower predischarge mortality than a restricted target (SpO_2, 85% to 89%) although no difference has been observed in longer-term outcomes (death or disability at 24 months).[23]

The off-label use of inhaled nitric oxide (iNO) in premature infants increased substantially from 2000 to 2008, with the greatest increase among infants born at 23 to 26 weeks' gestation.[24] Randomized controlled trials have evaluated the efficacy of routine administration of iNO in preterm infants with GA $\leqslant 34$ weeks to prevent BPD with varying results; meta-analyses have failed to demonstrate improved survival free of BPD.[24] Meta-analyses of individual patient data ($N=3298$) from trials in preterm infants (GA <37 weeks) at risk for BPD found no significant effect of iNO on death or BPD (59% vs 61%; relative risk (RR): 0.96; $P=0.11$) or severe neurologic events on imaging (25% vs 23%; RR: 1.12; $P=0.09$).[25]

Some evidence suggests that supplementing iNO with vitamin A or milrinone confers added benefit in premature infants with respiratory failure. A *post hoc* analysis of one large study, which randomized 793 mechanically ventilated infants (after stratification by birth weight) to placebo or iNO, showed that BPD was reduced in infants who received iNO plus vitamin A for the 750- to 999-g group compared with iNO alone ($P=0.01$). This group also showed reduction in the combined outcome of BPD/death compared with iNO alone ($P=0.01$).[26] There was an overall improvement in neurocognitive outcomes at the 1-year assessment in infants in the iNO plus vitamin A group compared with those in the iNO alone group. This improvement was mostly driven by the 500- to 749-g birth weight group.

Early HRF with persistent pulmonary hypertension of newborn occurs in the setting of PPROM and suspected pulmonary hypoplasia. Management includes a tailored approach with mechanical ventilatory support, consideration of early (off-label) use of iNO and serial evaluations by cardiac ultrasound.[27] A favorable response to iNO therapy in preterm infants born after PPROM and oligohydramnios has been reported in observational studies[12,28] and case reports.[10,11] A prospective nonrandomized study in 765 very preterm infants (GA $\leqslant 32.0$ weeks), which analyzed chest radiographs and airway specimens, found that 17 infants (2.2%) developed HRF, and in all cases, PPROM and oligohydramnios complicated the antenatal course.[12] All infants responded to iNO, regardless of major risk factors, such as early sepsis or prolonged PPROM starting before 24.0 weeks. The authors speculated that nitric oxide (NO) deficiency has a role in the pathogenesis of HRF following PPROM. Analysis of airway specimens detected low levels of proinflammatory cytokines and nitrite and nitrate in infants with HRF; however, they increased during iNO treatment and remained elevated after discontinuation of iNO. In a separate nonrandomized study in 26 infants (mean GA 27.8 weeks) with PPROM (GA <20 weeks) or rupture earlier than 25 weeks for more than 14 days, 5 newborns were stillborn, one died shortly after birth and 20 were admitted to the neonatal intensive care unit (NICU). All six who received high-frequency ventilation and iNO therapy survived to discharge.[28] Such survival rates with high-frequency ventilation and iNO compare favorably with historical controls (i.e., pre iNO/high-frequency ventilation). A favorable response to iNO has been reported in PH resulting from neonatal ibuprofen.[29,30] On the basis of the admittedly limited available evidence, targeted clinical management according to the underlying pathophysiology is a logical approach in this subgroup of preterm infants with HRF at risk of high mortality.[27]

There is some evidence that the percentage of preterm infants with PH responding to iNO increases with advancing GA. For example, a retrospective chart review compared preterm infants (GA <37 weeks) with PH in the first 4 weeks to matched controls without PH.[31] Almost half (44%) of the patient group had PPROM or oligohydramnios. A total of 37% (23/61) of infants with PH were treated with iNO; these infants were sicker and had a higher oxygen requirement and oxygenation index than those who did not receive iNO ($P<0.0001$). Infants with GA <29 weeks had a poor response to iNO (Figure 1). Infants with GA >29 weeks responded significantly better to iNO than infants born with GA <29 weeks ($P=0.009$). An improving trend in oxygenation (PaO_2) after iNO was also observed ($P=0.019$; $R^2=0.24$; Adj $R^2=0.20$) (Figure 2).

Thus, while the routine use of early iNO to prevent BPD is not supported by a preponderance of the evidence, and is not a US Food and Drug Administration-approved use of iNO, the use of iNO to treat early HRF with evidence of PH in preterm infants is a rational therapeutic option that may prove to be lifesaving in some infants. Indeed, guidelines for treatment of pediatric PH, published by the American Heart Association and American Thoracic Society in 2015, have recognized that iNO can be beneficial for preterm infants with severe hypoxemia primarily due to persistent pulmonary hypertension of newborn physiology, particularly if associated with PPROM and oligohydramnios.[32] This group of infants should be a focus of future study, although this is

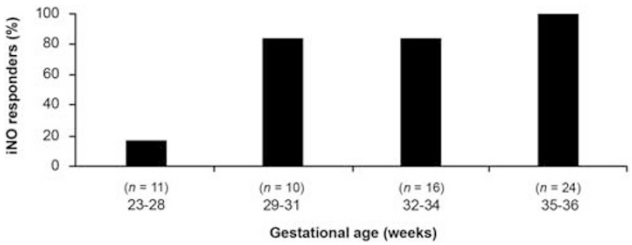

Figure 1. Response to inhaled nitric oxide (iNO) in infants with pulmonary hypertension across various gestational age groups in a retrospective chart review. Used with permission from Kumar *et al.*[31] Reprinted by permission from Macmillan Publishers, *J Perinatol,* 2007.[31]

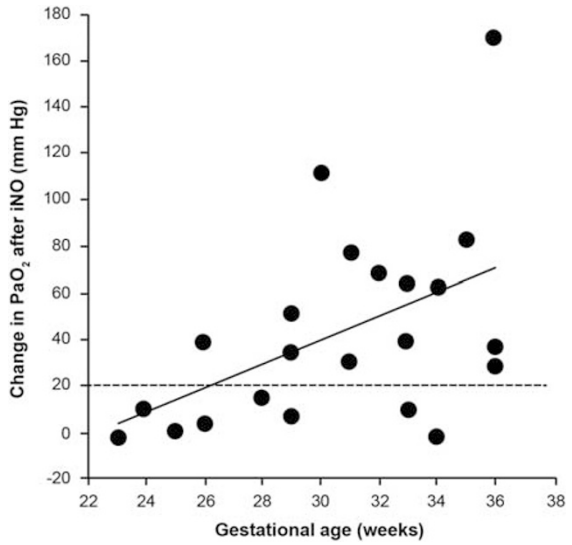

Figure 2. Linear regression plot of the change in arterial oxygen tension (PaO_2) following inhaled nitric oxide (iNO) for pulmonary hypertension across gestational age in a retrospective chart review. The dotted line at 20 mm Hg of arterial PO_2 separates the responders from non-responders to iNO. Used with permission from Kumar *et al.*[31] Reprinted by permission from Macmillan Publishers, *J Perinatol*, 2007.[31]

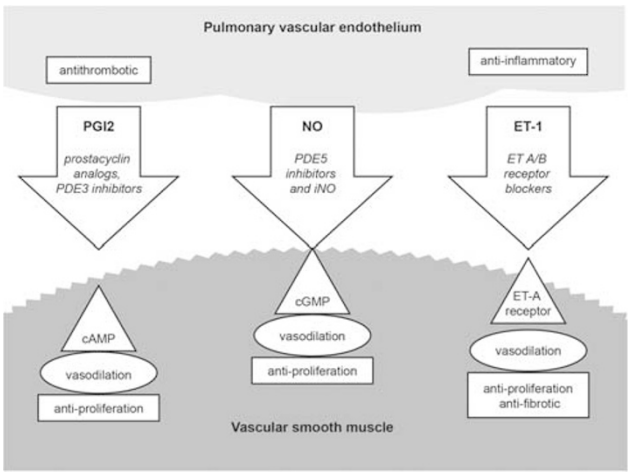

Figure 3. Pharmacotherapy for pulmonary hypertension. Schematic shows three major strategies (arrows) for both acute contraction state control and chronic remodeling of pulmonary vascular smooth muscle. Figure concept after Humbert *et al.* Used with permission from Collaco *et al.*[42] cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET-1, endothelin-1; ET-A, endothelin-A; iNO, inhaled nitric oxide; NO, nitric oxide; PDE3, phosphodiesterase-3; PDE5, phosphodiesterase-5; PGI2, prostacyclin.

a rare condition that will likely call for innovative research strategies.

Use of milrinone combined with iNO was associated with a reduction in the oxygenation index and iNO dose in a retrospective case review of infants (GA <32 weeks) who received milrinone for the treatment of PH and reduced right ventricular function.[33] Bosentan treatment, as an adjunct to iNO and oral sildenafil, has been described in a premature infant with severe persistent pulmonary hypertension of newborn after PPROM.[34] Single case reports of nesiritide[35] and intravenous adenosine have also been described in preterm infants with PH.[36]

Emerging technologies, such as automated respiratory support, lung assist devices and miniaturized oxygenators perfused like an artificial placenta, are the subject of investigation with the aim of improving outcomes in preterm neonates with respiratory insufficiency.[37,38] Additional therapies include caffeine and vitamin A, which have shown benefit in reducing BPD or death/chronic lung disease, respectively, in premature infants.[39,40] Interventions such as steroids, diuretics and bronchodilators have not been proven to have long-term efficacy and are associated with short- and long-term adverse effects in the preterm infant.

LATE HRF

HRF and PH that persist beyond the 28th postnatal day in preterm infants are typically considered to be 'late' HRF.

Compared with extremely low birth weight (ELBW) infants who do not develop late PH, ELBW infants with late PH have a lower birth weight, are smaller for their gestational age, received higher FiO_2 and frequently received prolonged mechanical ventilation.[6,7,41] In preterm infants, early PH (postnatal day 7) was a strong predictor for late PH at 36 weeks postmenstrual age (PMA) (RR: 2.85; 95% confidence interval (CI): 1.28 to 6.33) and greater BPD severity (RR: 1.12; 95% CI: 1.03 to 1.23).[7] Increasing BPD severity was associated with greater risk of PH.

Pulmonary vasodilators of various classes have been deployed in the clinical management of late PH in preterm infants, most extrapolated from their use in adults with PH. In an observational study of 145 ELBW infants (median GA 26 weeks), clinical practice for early or late PH included sequential or additive use of higher oxygen saturation limits, iNO, sildenafil, bosentan and epoprostenol.[6] No significant difference was observed between management practices in early or late PH, although the small sample size limited interpretation.

In premature infants with BPD, treatment of PH typically involves minimizing factors causing hypoxia (e.g., bronchospasm) and administering supplemental oxygen, although refinement of oxygen saturation targets in this specific patient population is needed. Inhaled prostacyclin, iNO and enteral sildenafil provide different avenues for modulating pulmonary vascular resistance (Figure 3).[42] The use of iNO to treat HRF and late PH in former preterm infants who are approaching term gestation is common practice in many NICUs. NO dilates vascular smooth muscle by increasing cyclic guanosine monophosphate levels, which are boosted by phosphodiesterase-5 inhibitors, including sildenafil. Prostacyclin relaxes vascular smooth muscle via increases in intracellular cyclic adenosine monophosphate levels, and phosphodiesterase-3 inhibitors, such as milrinone, stabilize the cyclic adenosine monophosphate concentration. Broad-spectrum blockers of endothelin A- or B-type receptors, such as bosentan, decrease vascular smooth muscle tone.

Evidence for the efficacy of pulmonary vasodilators in the BPD setting is limited to retrospective case series, and their risks versus benefits are not fully understood. In addition, pulmonary vasodilators should be used cautiously in BPD because of potential deleterious effects on common cardiopulmonary anomalies (e.g., patent ductus arteriosus, pulmonary vein stenosis, left ventricular dysfunction). Close monitoring is obligatory. In some circumstances, cardiac catheterization may be appropriate since echocardiography (ECHO) is not highly quantitative or sensitive for PH. In a retrospective review of 25 young children (age <2 years) with chronic lung disease (BPD, congenital diaphragmatic hernia or lung hypoplasia), ECHO estimate of systolic pulmonary artery pressure was 79% sensitive for the presence or absence of PH and 47% reliable for PH severity compared with cardiac catheterization measurements.[43] Cardiovascular anomalies commonly associated with PH are also difficult to detect on ECHO. A separate retrospective analysis of chart data, computed

Table 1. Evaluation of oral sildenafil for preterm infants with BPD-associated pulmonary hypertension[48–51]

	Mourani et al.[48]	*Nyp et al.*[49]	*Tan et al.*[50]	*Trottier-Boucher et al.*[51]
Study duration	2004–2007	2005–2009	2004–2012	2009–2013
Number of patients	25 (18 with BPD)	21	22	23
Gestational age [IQR]	28 weeks (range, 23–41)	27 weeks (range, 23–33)	25.6 ± 1.3 weeks	26 weeks [3]
Birth weight [IQR]	NR	641 g (460–1900)	631 ± 181 g	710 g [170]
Age at start of sildenafil [IQR]	184 days (range, 55–673) Pts with BPD	167 days (range, 83–307)	169 days [126–219]	106 days [85]
Concurrent therapy (*n*)	iNO (18) milrinone (4) bosentan (2)	iNO (11) milrinone (4)	iNO (1)	iNO (21) bosentan (2)
Improved RVSP, *n/N*	22/25 clinical improvement by ECHO	7/10	14/21 ⩾20% decline in RVSP	15/21
Improved respiratory support	NR	3/21	Reduction in FiO_2, no other changes	35% improved
Duration of therapy [IQR]	241 days (range, 28–950)	77 days (range, 8–135) for nonsurvivors	All survivors treated for at least 1 year	71 days [236]

Abbreviations: BPD, bronchopulmonary dysplasia; ECHO, echocardiographic; FiO2, fraction of inspired oxygen; IQR, interquartile range; iNO, inhaled nitric oxide; NR, not reported; RVSP, right ventricle systolic pressure.

tomography images and catheterization data revealed cardiovascular anomalies in two-thirds of patients with BPD and moderate or severe PH.[44]

If cardiac catheterization is not performed, careful monitoring is needed to detect deterioration in pulmonary performance after initiation of a vasodilator. Clinical practice in some centers is to perform cardiac catheterization if no improvement is seen after two medications. Cardiac catheterization may be especially useful for evaluation of left ventricular dysfunction and vasoreactivity testing to oxygen and iNO. Monitoring select biomarkers may also have an increasing role in early diagnosis and throughout the course of disease. Elevated levels of plasma asymmetric dimethylarginine (an endogenous inhibitor of NO production), endostatin (an antiangiogenic factor) and B-type natriuretic peptide have been detected in neonates with BPD and PH.[45–47] B-type natriuretic peptide was shown to be a prognostic marker of all-cause mortality in ELBW infants with BPD-associated PH.[47]

Chronic oral sildenafil therapy for BPD-associated PH has been evaluated in several retrospective studies (Table 1). Mourani and colleagues[48] evaluated enteral sildenafil (1.5 to 8.0 mg/kg/day) in 25 infants with chronic lung disease and PH. Most (18/25) infants had BPD. The median age at initiation of sildenafil therapy for infants with BPD was 184 days, with no patient started prior to 40 weeks' PMA. Three-fourths (18/25) of infants received concurrent iNO while other medications included diuretics, systemic steroids, milrinone or bosentan. Most (22/25; 88%) infants showed clinical improvement by ECHO after a median treatment duration of 40 days on sildenafil. In the 13 patients with interval estimates of systolic pulmonary artery pressure by ECHO, there was a significant decrease in both the absolute systolic pulmonary artery pressure ($P < 0.001$) and ratio of systolic pulmonary artery pressure and systemic systolic blood pressure ($P < 0.001$) after treatment. Eleven of those 13 patients (85%) showed at least a 20% improvement in this ratio. Although the time to improvement was variable, many of the infants were weaned off mechanical ventilator support and other PH therapies during sildenafil treatment without worsening of PH. Only two patients stopped or interrupted sildenafil therapy because of adverse events (recurrent erections, intestinal pneumatosis). Five patients (20%) died during the follow-up period, four of which were withdrawn from respiratory support due to respiratory futility or neurologic devastation and one had sepsis.[48]

A retrospective analysis by Nyp *et al.*[49] found that chronic oral sildenafil citrate therapy initiated at median 167 days for a median duration of 77 days in 21 infants (median GA 27 weeks) with severe BPD-associated PH produced a significant reduction in median echocardiographic pressure (65 vs 53 mm Hg, $P = 0.01$), although gas exchange did not improve in the first 48 h (Figure 4).[49] At the time that sildenafil was started, 11 infants were being administered iNO and four were receiving milrinone.

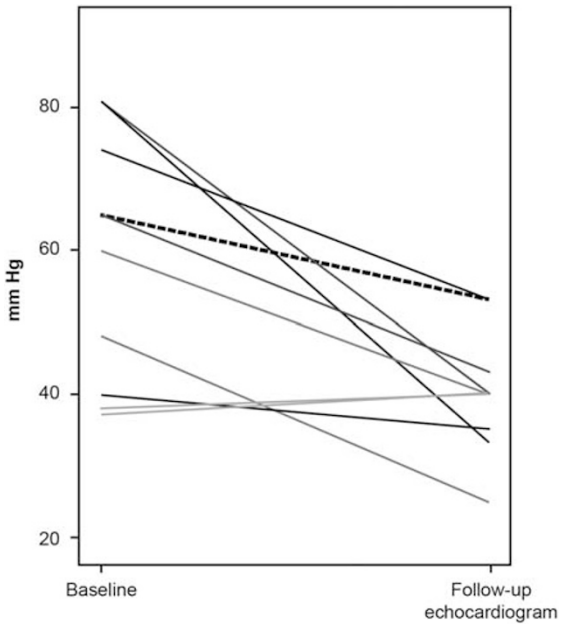

Figure 4. Effects of sildenafil citrate on echocardiographic (ECHO)-estimated right ventricular peak systolic pressure in infants with suspected pulmonary hypertension. The baseline measurement was the estimated right ventricular peak systolic pressures by ECHO closest to starting sildenafil citrate. The follow-up measurement was estimated right ventricular peak systolic pressures by ECHO occurring within 28 days of therapy initiation. The median right ventricular peak systolic pressure is represented by the black dotted line. The other lines represent individual changes in estimated right ventricular peak systolic pressures. Used with permission from Nyp *et al.*[49] Reprinted by permission from Macmillan Publishers, *J Perinatol*, 2012.[49]

Tan *et al.*[50] reviewed medical records and ECHO data from 22 infants (mean GA 26 weeks) who were administered oral sildenafil for BPD-associated PH. The mean age at the start of sildenafil therapy was 169 days. All survivors were treated for at least 1 year. Significant improvement in ECHO markers of PH was observed

4 weeks after initiation of therapy. Right ventricular systolic pressure significantly decreased (56.5 vs 34.3 mm Hg, $P < 0.001$) with two-thirds (14/21) of infants showing a $\geqslant 20\%$ decrease. The FiO_2 decreased significantly from 0.57 to 0.42 ($P = 0.02$), and the reduction in pulmonary vascular resistance was also significant ($P = 0.0003$). Left ventricular fractional shortening did not change significantly. No serious adverse effects were noted.

Trottier-Boucher *et al.*[51] similarly reported findings from a retrospective review in which 23 infants (median GA 26 weeks) with PH associated with BPD were administered sildenafil. A median dose of 4.4 mg/kg/day was started at a median age of 106 days and continued for a median duration of 71 days. Significant ECHO response (20% decrease in tricuspid regurgitation gradient or $\geqslant 1°$ change in septal flattening) was noted in 71% of cases, although clinical response (20% decreases in respiratory support score or oxygen requirements) was observed in 35% of cases. Most clinical responses were observed in the first 48 h of treatment, and the median time to observe an ECHO response was 19 days. Transient hypotension was the main reported side effect and occurred in 44% of the study population.

Other experimental therapies for PH such as intravenous sildenafil,[52,53] prostaglandin analogs including inhaled iloprost,[54–56] and subcutaneous treprostinil[57] have been presented in multiple case series and/or retrospective reviews, but no large series have been reported.

THE CASE FOR EARLY DETECTION AND BIOMARKER DISCOVERY

Clinical experience suggests that a potential approach to management of late HRF and PH involves earlier identification and risk stratification as well as more complete understanding of the pathophysiology of BPD. Greater insight into the spectrum of disease represented by BPD can optimize existing therapies and facilitate individualized treatment in addition to promoting the development of new therapies. BPD was traditionally considered a chronic form of lung disease in neonates treated with oxygen and positive pressure ventilation. Understanding of the nature of BPD, however, has evolved from the 'classic' or 'old' definition characterized by airway injury, inflammation and parenchymal fibrosis into a 'new' form characterized primarily by arrested alveolar and vascular development.[58] From an operational perspective, BPD was defined by Shennan *et al.* in the 1980s by the requirement for supplemental oxygen at 28 days of life. Subsequently, oxygen dependence at PMA 36 weeks was adopted as a diagnostic criterion because of better correlation with adverse longer-term pulmonary outcome.[59]

As NICU care practices have evolved, the concept of 'new' BPD has been embraced to highlight the histopathological failure of alveolar and vascular development. In 2000, a National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute (NHLBI)/Office of Rare Diseases (ORD) Workshop further reinforced the concept of 'new' BPD manifesting developmental arrest rather than inflammation and fibrosis. This 'NIH consensus' definition captured criteria from previous definitions and incorporated a stratification system based on the degree of BPD severity in infants born at GA $\leqslant 32$ weeks.[60] In 2003, a 'physiological' definition of BPD was added that included criteria for an oxygen reduction test or 'room air challenge' to standardize the determination of oxygen requirement at PMA 36 weeks across centers and individual patients.[61]

While definitions of BPD based on the need for supplemental oxygen at PMA 36 weeks provide a useful reference point, they are ill suited for predicting longer-term outcomes and for evaluating the multifactorial nature of BPD. Increasing evidence suggests that BPD is not one disease, but reflects multiple axes of disease development: parenchymal, airway and/or vascular. Some infants have primarily parenchymal disease whereas others display a significant component of airway disease (tracheobronchomalacia, obstruction, small airway disease) or pulmonary vascular disease. Indeed, infants with BPD exhibit varying combinations of clinical and pathologic features. In addition to changes in the definition of BPD, patient populations and clinical practices, particularly in the approach to use of supplemental oxygen and flow via nasal cannula or heated, humidified devices, have changed over time as well.

There is also heterogeneity in the underlying genomic background of BPD according to a recent integrated genomic analysis. A genome-wide scan was conducted on 1.2 million genotyped single-nucleotide polymorphisms and an additional 7 million imputed single-nucleotide polymorphisms, using a DNA repository from 751 ELBW infants (mean GA 26 weeks) including 428 who developed BPD or died.[62] Genome association and gene set analysis were performed for the categories of any BPD/death, severe BPD/death and severe BPD in survivors. Of the approximately 7650 gene sets evaluated, 75 pathways were significant ($P < 0.001$ and false discovery rate < 0.1) for BPD/death versus no BPD comparison.[62] A total of 95 pathways were significant for severe BPD/death and 90 for severe BPD in survivors. Notably, only three pathways overlapped all three categories, underscoring the fact that infants with BPD represent a very diverse and heterogeneous cohort whose genetic predispositions differ among those with mild/moderate and severe disease. The difference in clinical phenotype between mild and moderate BPD versus severe BPD is marked at the genomic level. In addition, there was little overlap in the major pathways associated with BPD/death between racial/ethnic groups.

The phosphorus oxygen lyase pathway (which includes adenylate and guanylate cyclases regulating cyclic adenosine monophosphate and cyclic guanosine monophosphate) was the top pathway associated with severe BPD/death ($P = 5.68^{-08}$, false discovery rate 0.00019) as well as severe BPD in survivors ($P = 3.91^{-08}$, false discovery rate 0.00013).[62] In addition to the involvement of known pathways (e.g., phosphorus oxygen lyase activity) and molecules (e.g., CD44) involved in lung development and repair, the analysis also identified novel pathways (e.g., targets of miR-219) and molecules (e.g., ADARB2, CD44) that may be involved in a genetic predisposition to BPD or death.

The findings from this genomic analysis underscore that operational definitions of BPD based on oxygen requirement do not capture the phenotypic and genetic diversity of BPD. Distinct biologic pathways are likely involved in the pathogenesis of mild and moderate BPD compared with severe BPD or death. Although BPD has a strong genetic component, conventional single-marker approaches have not successfully explained more than a small fraction of the heritability of BPD. Therefore, it may be more useful to evaluate multiple pathways rather than single single-nucleotide polymorphism or genes.

COMPREHENSIVE MULTIDISCIPLINARY APPROACH TO RESPIRATORY DISORDERS IN PRETERM INFANTS

From the clinical perspective, the multifactorial and heterogeneous nature of BPD poses challenges in the selection, timing and integration of treatment. Moreover, the lack of physiological, biochemical and genetic biomarkers in BPD and other respiratory disorders in preterm infants constrains early intervention and quantification of disease severity. The NHLBI-supported Prematurity and Respiratory Outcomes Program (PROP) provides a comprehensive multidisciplinary framework to characterize NICU and post-NICU discharge outcomes using genetic, environmental, physiological and clinical data as well as large databases of patient samples (including a repository of DNA and tracheal aspirate and urine samples) (Figure 5).[63]

The PROP involves a consortium of six clinical centers (incorporating tertiary NICUs at 13 sites) and a data coordinating

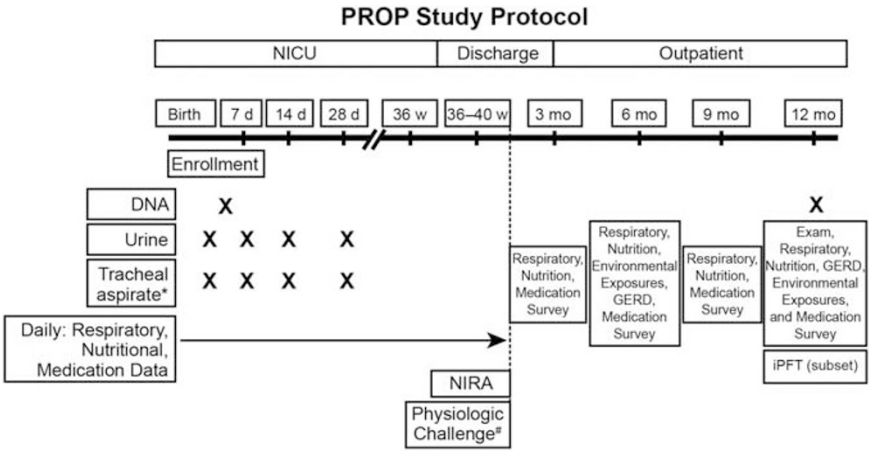

Figure 5. Prematurity and Respiratory Outcomes Program (PROP) study[63] protocol time line of health data and biospecimen collection spans from birth to 1 year corrected age. *Tracheal aspirate samples were collected if the infant was intubated and clinically required suctioning. #Physiologic challenge testing was either from oxygen to room air (21% oxygen, the 'room air challenge') or from room air to 15% oxygen ('hypoxia challenge') depending on status. NICU, neonatal intensive care unit; NIRA, non-invasive respiratory assessment; GERD, gastroesophageal reflux disease; iPFT, infant pulmonary function testing. Used with permission from Pryhuber *et al.*[63]

center. By characterizing the pathobiology of respiratory disease in extremely low GA newborns through 1 year of age at the molecular, biochemical, cellular and genomic levels, the PROP aims to develop objective biomarkers and outcome measures of respiratory morbidity in survivors of extreme prematurity (GA <29 weeks) beyond NICU hospitalization, leading to a better understanding of the nature and natural history of neonatal lung disease and of potential mechanistic and therapeutic targets.

A total of 835 infants have been enrolled in PROP and 765 (mean GA 26.7 weeks) have been assessed for BPD.[63] Of those assessed for BPD, 682 infants were in the study hospital at PMA 36 weeks and 315 were hospitalized at PMA 40 weeks. The frequency of BPD diagnosis in this cohort was noticeably different using strict Shennan (40.8%), Workshop (58.6%) or physiologic definitions (32.0%) of BPD, which underscores diagnostic challenges. The frequency of unclassified infants using strict definitions also ranged from 11.0% using the Shennan definition to 2.1% using the Workshop definition to 16.1% using the physiologic definition. The use of practical modifications of the Shennan definition decreased the number of unclassified infants.[64]

Creation of a robust, multidimensional data set from PROP and other initiatives will enhance understanding of the pathobiology of respiratory disorders in preterm infants. In addition, these data can facilitate earlier diagnosis of infants most likely to have a poor outcome and resolve questions such as the relevance of 36-week outcomes in lower GA infants. Future studies should be designed to include identification of physiologic or biochemical markers of disease susceptibility, genetic or biochemical markers of response to therapy, and surrogate endpoints that correlate with long-term outcomes.

CONCLUSION

In summary, multiple therapies including iNO, sildenafil and endothelin blockers, such as bosentan, have been evaluated in studies or described in case reports. Limited cohort size and weak study designs limit strong conclusions about safety and efficacy for the management of HRF and PH in preterm infants. Multicenter randomized controlled trials and contributions to existing pediatric PH data registries are needed to further improve the management and outcomes for infants and young children with HRF and PH.

Clinical experience and preclinical data in animal models suggest that earlier identification and risk stratification are needed to optimize outcomes. ECHO screening (with or without cardiac catheterization) might allow earlier initiation of therapy while risk stratification enables existing and novel therapies to be assigned for those at highest risk. A major challenge to improving outcomes is that current operational definitions of BPD (and other respiratory conditions) do not capture phenotypic and genetic heterogeneity. Better understanding of phenotype, genotype and 'omic' biomarkers may suggest potential targeted 'personalized' interventions. As such, there remains an urgent need for sensitive and specific indicators to help stratify patients for more tailored healthcare in this area. Initiatives such as PROP can provide such a framework to address these challenges through detailed analysis of hypothesis-driven biomarkers and post-NICU discharge outcomes.

CONFLICT OF INTEREST

JLA and NA received honoraria for their participation in a roundtable meeting supported by a grant from Mallinckrodt Pharmaceuticals, formerly Ikaria. JLA owns stock in Gilead, and is named on an intellectual property rights patent for the use of intravenous citrulline for neonatal lung diseases. NA has received research support from Pfizer, and has received research support as a mentor from Ikaria. NIH Grants: 1U01HL101456 (JLA); U01 HL122626 and R01 HD067126 (NA).

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