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Frontiers in Pulmonary Hypertension in Infants and Children With Bronchopulmonary Dysplasia

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Summary

Pulmonary hypertension (PH) is an increasingly recognized complication of premature birth and bronchopulmonary dysplasia (BPD), and is associated with increased morbidity and mortality. Extreme phenotypic variability exists among preterm infants of similar gestational ages, making it difficult to predict which infants are at increased risk for developing PH. Intrauterine growth retardation or drug exposures, postnatal therapy with prolonged positive pressure ventilation, cardiovascular shunts, poor postnatal lung and somatic growth, and genetic or epigenetic factors may all contribute to the development of PH in preterm infants with BPD. In addition to the variability of severity of PH, there is also qualitative variability seen in PH, such as the variable responses to vasoactive medications. To reduce the morbidity and mortality associated with PH, a multi-pronged approach is needed. First, improved screening for and increased recognition of PH may allow for earlier treatment and better clinical outcomes. Second, identification of both prenatal and postnatal risk factors for the development of PH may allow targeting of therapy and resources for those at highest risk. Third, understanding the pathophysiology of the preterm pulmonary vascular bed may help improve outcomes through recognizing pathways that are dysregulated in PH, identifying novel biomarkers, and testing novel treatments. Finally, the recognition of conditions and exposures that may exacerbate or lead to recurrent PH is needed to help with developing treatment guidelines and preventative strategies that can be used to reduce the burden of disease.

Keywords

pulmonary hypertension; bronchopulmonary dysplasia; prematurity; chronic lung disease

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INTRODUCTION

Owing to advances in neonatal care and technology, survival rates for extremely low birth weight (ELBW) infants have increased dramatically over the past several decades. However, many ELBW survivors continue to develop bronchopulmonary dysplasia (BPD), a condition characterized by impaired alveolar growth and airway inflammation.[1,2] Manifestations of BPD often include decreased pulmonary reserve (i.e., hypoxia, hypercarbia, and tachypnea) and airflow obstruction (i.e., wheezing and coughing). Although ELBW is associated with BPD,[3] there is significant variability in the severity and course of BPD even among infants of similar gestational age. Even in adulthood, impairments in respiratory health have been shown to persist and to be greater in BPD infants compared to infants born at term.[4]

In preterm infants, pulmonary hypertension (PH) may develop as a consequence of BPD and contribute to the severity and persistence of BPD symptoms. PH has been shown to impose additional morbidity and mortality on already vulnerable preterm infants with BPD. Although PH in the BPD population usually resolves with time and catch-up lung growth, increased mortality rates are associated with PH ranging between 14% and 38% in retrospective studies[5–9] and 12% in one prospective study.[10] Understanding the relationship between BPD and PH may help minimize the detrimental impact of these conditions on health outcomes.

The diagnosis of PH after 2 months of age in preterm infants is often associated with severe BPD. However, not all infants with PH have severe BPD,[5,6,11] which suggests that the impact of impaired alveolar growth on pulmonary vascular growth is variable. The development of PH is likely influenced by conditions that impact lung growth and function in utero and postnatally. Epigenetic, genetic, and environmental factors are also likely involved in the development of PH, but have not been extensively studied in this population. In this review we describe what is known about the burden, risk factors, pathophysiology, diagnosis, and management of PH in preterm infants with BPD as well as current gaps in our knowledge and future directions that should be explored (Table 1).

BURDEN OF DISEASE

Recently the tracking outcomes and practice in pediatric pulmonary hypertension (TOPP) registry reported that 12% of PH cases were associated with respiratory disease, with BPD being the most common cause.[12] This may be an underestimate since most registry participants were diagnosed by catheterization, and most preterm infants are diagnosed via echocardiogram. Underestimation of the prevalence of PH due to BPD may also occur since no ICD-9 code exists that encompasses this diagnosis. In the absence of large prospective studies, the incidence of PH in infants and children with BPD is unknown.[7,11] The only published prospective study from a single perinatal center found that 18% of ELBW infants were diagnosed with PH prior to discharge.[10] Retrospective studies report that PH may occur in up to 17–43% of preterm infants with BPD.[5–7,9] Prospective data on the natural course of disease, including time to resolution and rates of recrudescence, are also limited.[11] Retrospective data suggest resolution may occur as early as 4–5 months of age on average.[6] Large multicenter prospective studies are required to determine the incidence and course of disease, particularly as regional variability in BPD incidence and treatment strategies may exist.

It appears likely that PH adds additional healthcare costs for longer initial NICU stays, medical therapies and procedures. One retrospective study found that preterm infants with PH spent at least three additional weeks in the hospital.[6] There are also no data on the quality of life in preterm infants with PH and their families, but it is likely to be affected by longer hospitalizations, more frequent outpatient encounters, medication burden, and the

increased need for respiratory support. Data on long-term outcomes on these patients are lacking and it is unknown whether these infants will be at increased risk for the recrudescence of PH and/or chronic lung disease in later life.

RISK FACTORS FOR DISEASE

Risk factors for the development of PH are poorly understood.[7] Birth weight and severity of BPD play a role, although the magnitude of their contributions is unclear as not every ELBW infant with severe BPD develops PH.[5–7,11] Infants that are born small for gestational age (SGA) have been reported to be at higher risk for developing PH compared to non-SGA infants.[5,7,10] However, it is not known whether the small pulmonary vascular bed in SGA infants, an SGA-associated in utero exposure (e.g., poor maternal nutrition, drug exposures including anti-depressants or secondhand smoke exposure), or some other factor common to SGA infants contributes to the development of PH.

The structural abnormalities and decreased surface area of the BPD lung along with functional abnormalities such as persistent ventilation-perfusion mismatch, intermittent hypoxia and/or hypercarbia,[13] and poor airway clearance all may contribute to PH development. Any factor that hinders lung growth and recovery may increase the risk of the development of PH. Such factors may include positive pressure ventilation, dysphagia, gastro-esophageal reflux, respiratory infections, and suboptimal nutrition.[6] In addition, concomitant lung disease such as surfactant disorders or interstitial lung diseases may also contribute to the development of PH. Further research is needed to identify infants with lung disease who are at the highest risk, including infants who are difficult to extubate, require frequent courses of systemic steroids, or have difficulty gaining weight.[7]

Maternal pre-eclampsia may also be a risk factor for PH in the preterm infant. Mothers with pre-eclampsia have been shown to have elevated serum and amniotic fluid levels of soluble VEGF receptor 1, also known as sFlt-1.[14] sFlt-1 antagonizes the VEGF-VEGFR2 signaling pathway, thus interfering with endothelial maintenance and cell growth. Administration of sFlt-1 into amniotic fluid in rats has been shown to lead to decreased alveolar growth and pulmonary vessel density in the offspring.[15] As demonstrated in a murine model, sFlt-1 may lead to vascular dysfunction and poor endothelial growth through an imbalance between the endothelial system and eNOS.[16] Further understanding of these pathways in the preterm infant may help identify therapies that could potentially prevent PH development in preterm infants.

Associations between oligohydramnios and PH have also been reported in two retrospective studies of preterm infants with BPD.[5,8] We have observed that pulmonary hypoplasia from premature rupture of membranes and prematurity appears to increase the risk of PH (Fig. 1). Other potential risk factors may include shunts that increase pulmonary blood flow (e.g., intracardiac shunts, large collateral vessels, or PDAs)[6,17,18] and upper or lower airway anomalies that hamper effective gas exchange (e.g., subglottic stenosis, tracheomalacia, etc.).[11,17] Other postnatal exposures which require additional study in the preterm population include postnatal secondhand smoke exposure[19] and systemic inflammation.[8]

PATHOPHYSIOLOGY OF DISEASE

Classification of Pediatric PH

The variation in clinical presentation of PH is partially dependent on the contributions of different vascular elements, which is reflected in a recently proposed classification of PH within BPD.[13] Lesions upstream of the pulmonary vascular bed, such as patent ductus arteriosus and left-to-right intracardiac shunts may contribute to PH in the preterm infant.

Within the lungs, impaired lung growth is often associated with a small pulmonary vascular bed, giving a "fixed" component of PH. However, some of these children have a "responsive" component consisting of pulmonary arterioles that respond to vasodilator therapies such as nitric oxide, sildenafil, bosentan, and iloprost (Fig. 2).[20] Lastly, downstream pulmonary venous lesions and left ventricular dysfunction may also contribute to PH as well. The physiological interplay between these components in the preterm infant is poorly understood. However, earlier gestation infants (<29 weeks gestation) may have more of a fixed component than later gestation infants as suggested by different response rates to nitric oxide therapy.[8] Thus, recognizing the relative contribution of vascular components to PH will be crucial in optimizing management as an infant with predominantly "responsive" disease will respond to vasodilators, one with predominantly "fixed" disease may not, and one with a significant venous lesion may actually worsen with vasodilator therapy.

BPD and PH

Impaired alveolar development is associated with extreme prematurity, but postnatal factors such as neonatal infections, initiation of positive pressure ventilation, exposure to hyperoxia, and poor nutrition can also significantly impair lung growth. Even though significant alveolar catch up growth in the postnatal period is possible, many children with a history of prematurity and BPD have abnormal lung function and exercise intolerance in later life.[21–23] Small airway disease is often a dominant clinical phenotype in both early and later life in the child with BPD; however, it is unknown whether small airway dysfunction is associated with or can exacerbate or worsen PH. Another concern is whether children with BPD are at greater risk for late-onset pulmonary vascular dysfunction. O'Reilly and colleagues found that exposure to neonatal hyperoxia caused pulmonary vascular disease and premature mortality in aged mice.[24] Longitudinal studies are needed to determine if preterm infants are at increased risk for early onset cardiopulmonary disease in adult life.

Inflammation and oxidative stress are believed to be important contributors to BPD severity,[25] which may be mediated through exposure to hyperoxia.[26–29] Although increased levels of inflammatory cytokines have been reported in preterm infants who subsequently developed BPD,[2] it is unknown whether inflammatory cytokines independently contribute to the development of PH. Similarly, the impact of oxidative stress on the pulmonary vasculature of the preterm infant has not been extensively studied. Endothelial cells are susceptible to oxidative stress and increased oxidative stress can induce vascular pathology in many adult diseases.[30] Compounding the effect of increased oxidative stress, preterm infants are often deficient in antioxidant reserves, thus increasing their risk of oxidative stress induced injury. It has been suggested that supplementation with both enzymatic and non-enzymatic antioxidants may be helpful in reducing oxidative stress in the preterm infant.[31] A study in mice found that activation of the transcriptional factor Nrf2 protected neonatal mice exposed to hyperoxia through the induction of antioxidant pathway genes.[32] Along those lines, further study into interventions that induce activation of antioxidant pathways prior to an oxidative stress, may be warranted.

Molecular Pathophysiology

In vitro work has demonstrated that nitric oxide is necessary for normal growth, proliferation, migration, and tube formation of fetal pulmonary artery endothelial cells.[33] Although routine use of inhaled nitric oxide in preterm infants is currently not recommended,[34,35] selected use of nitric oxide on preterm infants with PH or at high risk of developing PH may still be of benefit.[8] Arginases I and II compete with nitric oxide synthase (NOS) for L-arginine and specific inhibition of arginase in human endothelium has been shown to increase nitric oxide production.[36] An imbalance between arginase II and NOS in the preterm lung may partially account for the development of PH in the preterm

infant. Supplementation with L-citrulline may be a potential therapy to consider, as it has been shown to decrease arginase activity, increase arginine and nitric oxide levels, and rescue a BPD phenotype in a neonatal rat model.[37] Further work on the nitric oxide pathway and other pathways identified by genetic or biomarker screening is needed to elucidate the molecular pathophysiology of PH in the BPD infant.

Genetic and Epigenetic Factors in PH

The contribution of genetic and/or epigenetic factors to the development and severity of PH in infants with BPD is currently unknown. It is plausible that such mechanisms contribute to the development of PH, as susceptibility to developing BPD has a strong heritable component based on twin studies.[38,39] Identifying causal or modifier genes of BPD and PH may eventually serve as a tool for identifying infants at risk of developing PH. A number of loci have been implicated in BPD susceptibility through candidate gene association studies, including the genes encoding surfactant proteins B and D, TNF-α, mannose binding lectin, angiotensin converting enzyme,[40] and TLR5,[41] but no single locus has been consistently associated with BPD in general or PH specifically. Recently, *SPOCK2* gene polymorphisms were found to be associated with BPD in a genome-wide association study.[42] The function of this protein is unknown, but its expression pattern during development and within the lung supports a potential role in BPD pathogenesis. Specific lung diseases known to have a genetic basis, such as surfactant dysfunction disorders and alveolar capillary dysplasia, should be considered in infants with unresponsive PH, particularly those in which severity of lung disease seems out of proportion to what might be expected based upon their gestational age and postnatal course. Future research should include identifying modifier genes through exome and genome-wide analyses, candidate SNP studies of genes involved in familial pulmonary arterial hypertension (e.g., *BMPR2, ENG*, and *ALK1*),[20] and gene sequencing for loss of function mutations in the evaluation of specific candidate genes.

Studies linking the development of PH with epigenetic changes in the neonate are limited. A study by Koukoura et al.,[43] has shown an association between DNA methylation and decreased expression of IGF2, a gene involved in placental and fetal growth. A study in chronically hypoxic hypertensive calves also demonstrated a link between epigenetic changes and vascular remodeling.[44] They found increased class I histone deacetylases activity associated with increased inflammatory gene expression in adventitial fibroblasts isolated from hypoxic hypertensive calves compared to controls. A better understanding of the genetic basis of PH in the BPD infant may allow for the identification of biomarkers that could be used in diagnosing and guiding therapy.

DIAGNOSIS OF DISEASE

PH may manifest through physical findings such as parasternal lift, quality of the second heart sound, or evidence of right heart failure. Chest radiography findings can include cardiomegaly, right atrial, and right ventricular dilatation and enlarged central arteries with electrocardiogram findings of right axis deviation or right ventricular hypertrophy. However, these findings may be non-specific and often subtle in the small infant, leading to the need for better diagnostic modalities.[6,17,45] Non-invasive studies for PH diagnosis should first be considered to minimize procedural complications that can occur with cardiac catheterization.

Echocardiograms in Diagnosis of PH

In practice, echocardiograms (echo) are frequently used to both screen and follow PH in children with BPD; however no guidelines exist for either screening selection or follow-up intervals in this population.[7,17,18] Based on our experience and others, evaluation by echo

should be considered in all preterm children with BPD who require supplemental oxygen and/or need positive pressure ventilation beyond 2 months of age; special consideration should also be given to those who were SGA and are growing poorly. Children on vasodilator therapy for PH should undergo echo evaluation before weaning therapy or with pulmonary exacerbations. An echo should also be considered in children with BPD and a history of PH who fail to improve during an acute pulmonary exacerbation. Commonly used methods of assessing PH via echocardiography include quantitative methods such as tricuspid regurgitant jet velocity (TRJV), ventricular septal defect or patent ductus arteriosus velocity, pulmonary regurgitation velocity to estimate pulmonary artery end diastolic pressure, and qualitative measures such as interventricular septal position in systole, right ventricular hypertrophy, dilation, and/or dysfunction.[17] Of these methods, TRJV is the mainstay of pediatric right ventricular systolic pressure (RVSP) evaluation in clinical practice. Using the TRJV, the systolic pressure gradient between the right atrium and right ventricle (and hence the RVSP and inferred systolic PA pressure) can be estimated using the modified Bernoulli equation of RVSP = $4v^2$ (where v, velocity of the TR jet) plus the right atrial pressure.

Simultaneous measurements of echo TRJV (and calculated RVSP) with directly measured RVSP during cardiac catheterization in sedated adults demonstrated an excellent correlation ($r = 0.96$).[46] However, the strength of this correlation has not been borne out in pediatric data. Hill et al.,[47] recently assessed pediatric patients undergoing cardiac catheterization for a suspected diagnosis of PH (n = 127) within the Mid-Atlantic Group of Interventional Cardiology (MAGIC) registry and found a poor correlation ($R^2 = 0.36$, $P < 0.01$) between transthoracic echocardiographic estimates of RVSP based on TRJV and cardiac catheterization. However, the echo and catheterization data were not simultaneously obtained, and the majority of these patients were under general anesthesia. Mourani et al.[48] retrospectively analyzed the correlation between systolic PAP via nonsimultaneous echo TRJV and cardiac catheterization in 25 patients <2 years of age with chronic lung disease, and also found a poor correlation ($r = 0.19$, $P = 0.43$); however despite this poor correlation, echo correctly diagnosed the presence or absence of PH in 79% of the studies, giving a sensitivity of 88% and specificity of 33%. A major limitation of echocardiographic evaluation of TRJV is that it relies on adequately analyzeable TR regurgitant jet, which is not present in all patients. Mourani et al. described 61% of studies with adequate TR jet for analysis; Currie et al.[46] reported analyzeable TR in 80% of adults with elevated right ventricular pressure, and 57% of adult patients with normal right ventricular pressure.

Decreased sensitivity in assessing PH severity is a major limitation to using echo.[48] This may be due to chest hyperinflation, lack of cooperation, and small chest size.[11] In addition, pulmonary venous stenosis can be difficult to diagnose by echo.[49] Future studies in children using tricuspid annular plane systolic excursion (TAPSE), speckle tracking of the right ventricle, and 3D echo to evaluate right ventricular size and function, as well as inferior vena cava dilation ratio may provide additional insight into the diagnosis of PH and assessment of severity.

Cardiac Catheterization

Cardiac catheterization, offers the advantage of definitive and comprehensive information about cardiopulmonary hemodynamics and therapeutic drug testing. However, due to higher complication rates in pediatric patients, cardiac catheterization should only be performed in tertiary care centers that have cardiologists and anesthesiologists with experience in the care of these children.[50] There are no widely accepted guidelines that indicate which patients with BPD and PH should be catheterized. However, catheterization should be considered when the severity of PH is uncertain despite noninvasive assessment, when acute

responsiveness to pulmonary vasodilators must be assessed, when severe PH is not satisfactorily responding to therapy, and when vascular narrowings or shunt lesions must be assessed and/or treated. In one series, 31% of formerly premature infants with BPD and PH underwent cardiac catheterization.[7]

The catheterization WHO diagnostic criteria for PH are presently mean pulmonary artery pressure >25 mmHg [normal 14–16 mmHg], mean pulmonary capillary wedge pressure <15 mmHg, and pulmonary vascular resistance >3 mmHg/L/min (Wood units). The WHO criteria are based on adults and have been adapted to children, however as the systemic blood pressure is remarkably lower in neonates, the WHO criteria results in a proportionally higher right ventricular to left ventricular pressure ratio in infants than adults.

Acute hemodynamic responses to pulmonary vasodilators can be assessed and can inform decision-making about long-term use of such agents. Typically, baseline hemodynamic measurements are made while the patient is breathing air or no more than the patient's usual supplemental FiO_2. The FiO_2 is then increased to 100%, and the hemodynamic measurements are repeated. Nitric oxide in concentrations that may range between 20 and 80 parts per million is then added to the inspired oxygen, and hemodynamic measurements are repeated again. Responses to other agents such as intravenous or inspired prostacyclin analogues or enteral sildenafil can also be assessed in similar fashion. Responsiveness in pediatric patients is presently defined as a decrease in mean pulmonary artery pressure ≥20%, an increase or no change or only slight decrease in cardiac output, and decrease or no change in the ratio between pulmonary vascular resistance and systemic vascular resistance.[51]

The presence and degree of left ventricular dysfunction (systolic and diastolic) can be demonstrated and further guide medical management.[52] Precise information about pulmonary arterial and venous anatomy can be obtained using angiography. Peripheral pulmonary artery stenoses can contribute to right ventricular hypertension in these infants, and these can be assessed angiographically as well as hemodynamically. Rare disorders, which cause PH in infants, such as alveolar capillary dysplasia and primary pulmonary vein stenosis, can be identified. Information obtained during cardiac catheterization can guide decision making for surgical or transcatheter management of pulmonary arterial and venous narrowings and closure of shunt lesions: atrial septal defects, patent ductus arteriosus, or aortopulmonary collateral arteries. Such shunt lesions may be found in as many as 58% of patients undergoing cardiac catheterization.[48] Cardiac catheterization in children with BPD is labor-intensive, time-consuming, and expensive. There is also significant anesthetic risk associated with the procedure. Although one registry study showed that cardiac catheterization can be performed for pediatric PH patients with few (mostly technical) adverse events and zero mortality,[47] another retrospective study from a single center showed that resuscitation or death occurred in 6% of cases.[53] Thus, discretion is essential in selecting patients for referral for cardiac catheterization.

Biomarkers and Other Non-Invasive Testing for PH

Given the invasive nature of cardiac catheterization, there is a need to identify non-invasive modalities for diagnosis and follow-up, which may include circulating biomarkers. Although no biomarkers for PH in preterm infants have been identified at this time, strategies for identifying promising biomarkers may include testing adult biomarkers, such as osteopontin,[54] and novel discovery projects. The best studied PH biomarker is the cardiac hormone brain natriuretic protein (BNP) and its prohormone N-terminal pro-BNP (NT-proBNP). Levels of BNP have been shown to correlate with disease severity and prognosis in adults with PH.[55–57] However, BNP and NT-proBNP have been challenged as biomarkers in the infant with BPD as BNP is a cardiac protein, and thus an indirect measure of pH

associated with lung disease. BNP is developmentally regulated in the heart with levels peaking in the neonate and declining after birth reaching a more stable adult equivalent level after 2 years of age.[58,59] In normal children the median NT-proBNP (pg/ml) was 3,183 at 0–2 days of age, 2,210 at 3–11 days and 141 at 1–12 months.[58] Steady state adult range levels were not achieved until >2 years of age. Additional confusion with the use of BNP is the heterogeneity and lack of acceptance of a standard assay platform, resulting in widely divergent blood concentrations, making it challenging to compare studies from multiple institutions. Assays for NT-proBNP alone vary significantly as the reported mean difference between the Roche and Biomedica assays is 1,649 pg/ml.[59] Even with these caveats,[58,60] BNP or NT-proBNP levels may be useful in following response to treatment in infants older than 1 month of age and may support diagnosis of PH in neonates without congenital heart disease.[17] Discovery projects (e.g., proteomic screening) focused more on the lung and children may yield novel circulating biomarkers with improved diagnostic/prognostic efficacy of disease progression.

In addition, other studies may be useful in assessing factors contributing to PH severity. High resolution CT and CT angiograms performed in conjunction with an experienced pediatric radiologist can be used to assess parenchymal lung injury, pulmonary venous occlusive disease, and pulmonary vein stenosis. Abdominal ultrasound can be used to rule out abdominal malformations and portal vein obstruction that can be associated with PH.[50] In addition, as hypoxia and hypercarbia may worsen PH severity, assessing gas exchange in infants with PH and BPD prior to weaning supplemental oxygen may be helpful.[11] Office-based pulse-oximetry may not be adequate for all patients; we recently demonstrated that infants with BPD with normal awake oxygen saturations commonly had intermittent oxygen desaturations on overnight polysomnography.[61] Further study is needed to assess the risk of intermittent hypoxia/hypercarbia for PH before recommending overnight polysomnography as a more sensitive means of assessment.

MANAGEMENT OF DISEASE

There are no clinical guidelines for the treatment of PH in infants and children with BPD. Basic questions regarding PH management remain unanswered such as whether aggressive pulmonary management and vasodilator therapy attenuate morbidity and mortality. Contributing to the lack of guidelines are the limited number of clinical outcomes studies and the variable response of preterm infants to PH treatments. Over the last several years, there has been increasing off-label use of pulmonary vasodilators in the treatment of PH with little evidence to support their use.[18] When pulmonary vasodilator therapies are considered, we believe that they should be administered in consultation with a pediatric cardiologist. Sildenafil has been used in preterm infants with BPD and PH.[62–66] A recent study describing the use of sildenafil in infants with BPD and suspected PH reported an improvement in estimated right ventricular peak systolic pressure by echo, but no significant improvement in respiratory scores in the first 48 hr after initiation of sildenafil.[63] Another retrospective study of 25 children <2 years of age with chronic lung disease and PH found that 88% had hemodynamic improvement after a median of 40 days of treatment.[62]

Adequate management of respiratory symptoms is the mainstay of care for all BPD children including those with PH. Supplemental oxygen to maintain baseline oxygen saturations at 95% should be considered in preterm infants with PH and BPD, once the retinal vasculature is mature.[7,17,45,67] It is unknown whether BPD therapies such as diuretics, inhaled corticosteroids, chest physiotherapy, and bronchodilators can improve outcomes in BPD children with PH, however it is recommended that ventilation perfusion mismatch be minimized to avoid episodes of hypoxia and hypercarbia. Lastly, good nutrition is needed for lung growth, which may help optimize pulmonary vascular bed growth. In patients with

BPD and PH who do not improve with supportive measures, cardiac catheterization should be considered.[11,68–75] Cardiac catheterization can help direct medical therapy and it can be used to evaluate and close intracardiac shunts and collateral vessels that can worsen PH in the preterm infant.[18]

Other management strategies include ruling out or diagnosing conditions that can exacerbate PH in the BPD infant such as upper airway obstructive lesions or lower airway malacia.[18] Lower airway symptoms may exacerbate chronic PH; thus causes of lower airway inflammation should be aggressively managed. This includes appropriate immunoprophylaxis against respiratory syncytial virus, influenza, and pertussis.[11] An immunological evaluation should be considered in patients with recurrent fever and those exposed to prolonged steroid courses during infancy.[76] Aspiration of oral feeds or stomach contents can lead to chronic lung inflammation, which may lead to more severe PH; thus swallowing studies, upper gastrointestinal series, trials of nasogastric or nasoduodenal tube feeding, and antireflux medications should be considered.[18] In some cases gastrostomy tube placement and/or Nissen fundoplication may be required. Further research is needed to determine the contribution of orapharyngeal dysfunction to PH severity.

Although lung transplantation can be considered for irreversible PH in patients with BPD, lung transplantation during infancy is associated with increased mortality in the first year post-transplant compared to other pediatric age groups.[77] Exciting work however, is currently being done to evaluate the utility of prenatal interventions to attenuate PH. A recent study demonstrated improvement of PH in a rat model of congenital diaphragmatic hernia with the administration of antenatal sildenafil.[78] Another study of preterm infants found antenatal steroids to be protective against PH.[9]

Management of Pulmonary Hypertensive Crises

Pulmonary hypertensive crises may present with increased respiratory effort, increased hypoxemia, and circulatory or respiratory failure, or cardio-pulmonary arrest. These episodes can occur acutely and may require ICU-level care. Triggers most commonly include aspiration, infectious respiratory illnesses,[11] or anesthesia for cardiac catheterization or surgery.[79] A drop in alveolar oxygen tension may be the common denominator linking these inciting scenarios.[80] The ICU management of PH crises requires an integrative approach that focuses on the treatment of increased pulmonary vascular resistance and its impact on right ventricular function. In addition, when present and treatable, intercurrent infectious processes must be addressed as primary inciting causes of life-threatening deterioration. Successful sedation strategies in this setting are essential to control sympathetic outflow and avoid agitation that may interrupt mechanical ventilation during regular care and essential pulmonary toilet. Approaches that balance narcotic analgesia and dexmedetomedine infusions for sedation may be advantageous,[81,82] whereas boluses of benzodiazepines and the use of barbiturates may suddenly drop cardiac output and/or systemic vascular resistance. Neuromuscular blockade may be a helpful adjunct. Optimal mechanical ventilation incorporates PEEP and inspiratory times that reestablish and maintain functional residual capacity without regional overdistention that could elevate pulmonary vascular resistance. Mean airway pressures should be kept modest to maximize systemic venous return and preload delivery to the challenged right ventricle. There are limited data on the use of pulmonary vasodilator therapies with acute PH crises in infants with BPD, but agents such as inhaled prostacyclin and nitric oxide, and enteral sildenafil may provide avenues for modulating pulmonary vascular resistance (Fig. 2). Inhaled prostacyclin has been documented to result in a 30% mean drop in the oxygenation index of neonates with PH, albeit in the setting of meconium aspiration.[83] In another series, nebulized iloprost was found to be useful in preterm infants with respiratory failure and PH.[84] Airway reactivity however may limit the utility of inhaled iloprost in the BPD

population. In a study by Ivy et al.,[85] 22 children with PH were transitioned from IV prostanoids to inhaled iloprost. They found that 38% of children had a 15% drop or greater in $FEF_{25–75\%}$ with inhaled iloprost. Bosentan is another vasodilator used to treat PH however its longer length of time to achieve therapeutic levels, may limit its use during an acute hypertensive crisis.[80,86] Recently, though a randomized double-blind placebo-controlled study in infants with persistent PH of the newborn reported significant improvement in oxygenation within 6 hr of initiation of bosentan.[87] Inotropic support with milrinone may be useful for a patient with right- or bi-ventricular failure following PH crises and/or cardiac arrest that complicates chronic dysfunction of a pressure-loaded right ventricle. In addition, milrinone optimizes cyclic AMP concentrations in the smooth muscle cells of pulmonary resistance vessels by inhibiting type 3 phosphodiesterases.[88,89] The use of milrinone may also obviate or minimize the need for adrenergic agents whose deleterious consequences include chronotropic stimulation that may compromise filling time in the setting of a stiff right ventricle, and elevation of both systemic and pulmonary vascular resistance. Use of ECMO may be considered in a subset of cases where there is an identifiable and reversible proximate cause for the acute crisis.[83]

Anesthesia and the BPD Infant With PH

Infants with BPD with PH are at increased risk for PH crises while under anesthesia or sedation. The incidence of PH-related complications may be higher during cardiac catheterization than during non-cardiac procedures.[79] Anesthetic induction, procedural stimulation and emergence from anesthesia may all increase the risk of PH crisis due to physiological changes that can cause hypercarbia, hypoxia, increased catecholamine release, and acidosis.[90,91] The overall risk of cardiac arrest in children undergoing anesthesia has been estimated at ~1.4 per 10,000 cases[92] and a retrospective review in Denver showed a nearly sixfold increase in risk of perioperative/periprocedural cardiac arrest in children with PH.[79] This report further detailed the perioperative risks associated with PH including a 1.3% mortality rate and a 4.5% risk of major complications. Most complications occurred in patients that had suprasystemic pulmonary artery pressures documented preoperatively. Another review of over 100,000 anesthetic cases at a quarternary referral pediatric center reported that fully 50% of anesthetic-related deaths occurred in patients with PH, primarily in infants.[91] With careful collaborative preoperative planning that integrates surgical, cardiology, and cardiac anesthesiology expertise, even cardiac catheterization for children with PH can be relatively safe.[47] Judicious preoperative sedative premedication can decrease the risk of sympathetic stimulation during anesthetic induction and continuation of vasodilator therapies such as sildenafil and nitric oxide may prevent a PH crisis in the operating room. Management considerations during the critical induction period include the placement of all standard monitors, maintenance of adequate alveolar and arterial oxygenation, ample minute ventilation, protection of systemic blood pressure by careful administration of IV fluids and slow infusion of vasoactive induction agents, and the availability of adequate vascular access and inotropic support.[91] For optimal anesthetic maintenance in PH, a balanced technique incorporating inhalational agents, narcotics, and neuromuscular blockade is recommended. Controlled ventilation is indicated in order to reduce hypoventilation and the resultant hypoxia that may occur during spontaneous ventilation, however, adequate anesthetic depth must be ensured prior to placement of an endotracheal tube. Emergence from anesthesia is also challenging, and deep extubation of the trachea may be considered in order to decrease airway stimulation during emergence. Finally, postoperative care should incorporate PH therapy that is compatible with needs for continued NPO status, and some success with pre-emptive perioperative use of inhaled iloprost has been reported.[93]

CONCLUSIONS

Our understanding of the pathophysiology and management of PH in preterm infants is rapidly evolving. The prognosis remains difficult to predict and given that retrospective studies have demonstrated an increased risk of mortality, frank discussions of the risks associated with PH with families are warranted. At this juncture, comprehensive research strategies are needed to elucidate the pathophysiology of PH and develop guidelines for management. Due to the complexity of these children, we recommend a multidisciplinary approach to help improve outcomes. Equally important is the ongoing education of healthcare providers to recognize infants at risk for developing PH and management strategies for preterm infants with PH.

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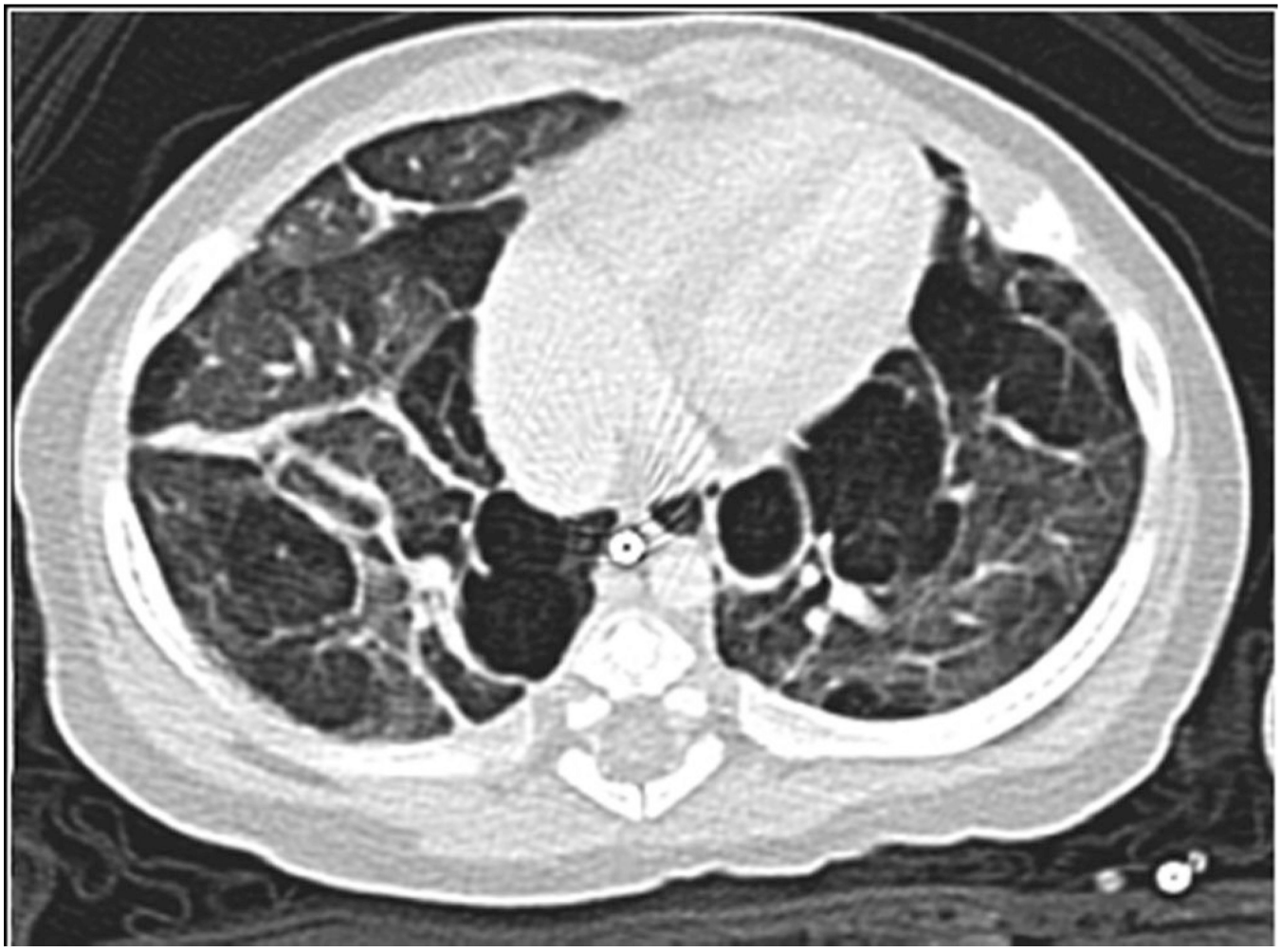

Fig. 1.

Chest CT scan of infant born at 26 weeks gestation with history of premature rupture of membranes at 22 weeks gestation. Although only briefly intubated in the NICU, the infant was found to have severe pulmonary hypertension and cystic emphysematous lung changes at 6 months of age.

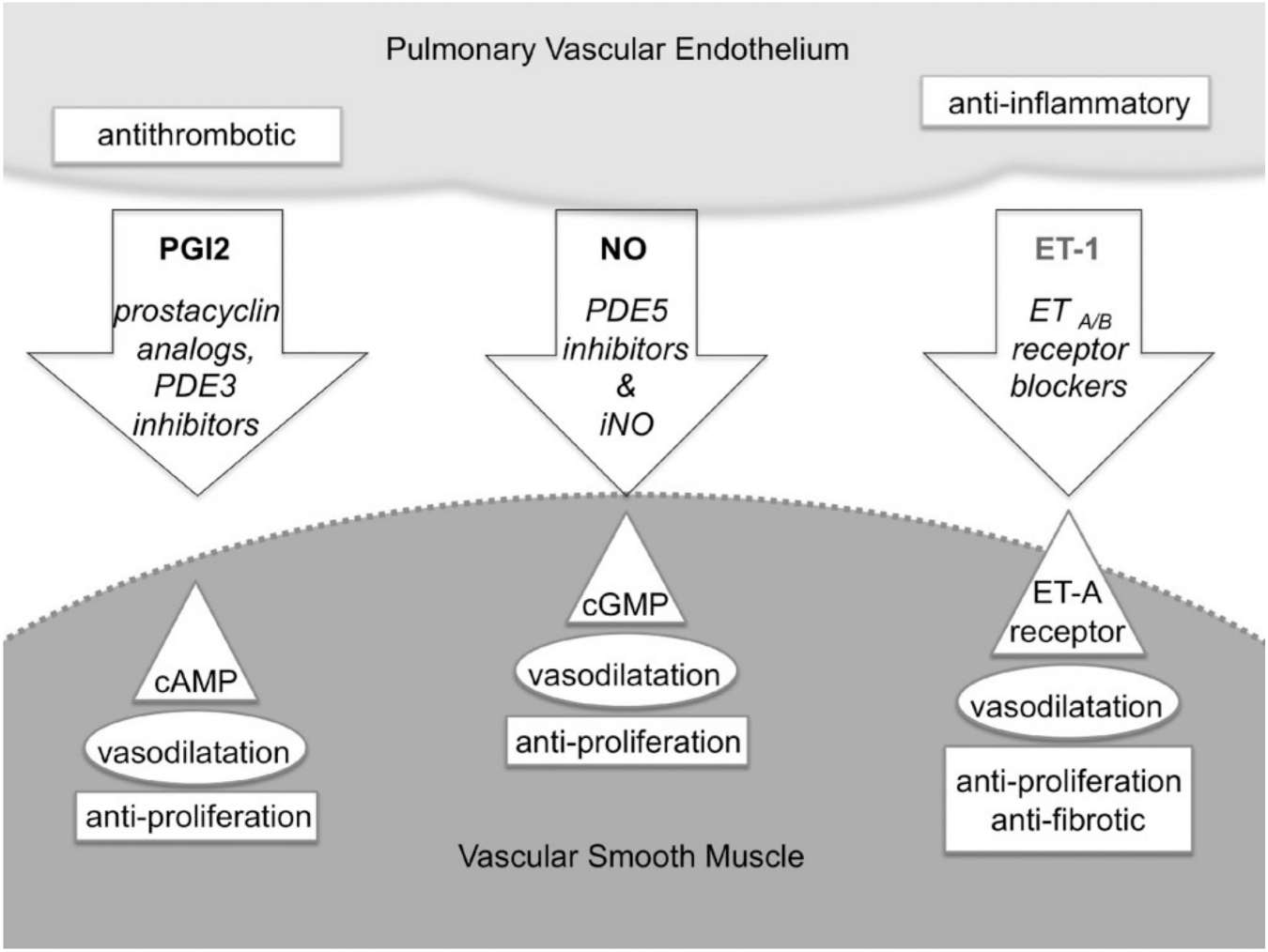

Fig. 2.

Pharmacotherapy for pulmonary hypertension. This schematic shows three major strategies (arrows) for both acute contraction state control and chronic remodeling of pulmonary vascular smooth muscle (SMC). All three strategies are derived from natural products of the pulmonary endothelium (PEC) that are shown in bold print at the tops of the arrows. Classes of therapeutic agents are shown in italics in each arrow. Principal molecular targets of each pharmacotherapeutic strategy are shown in triangles, acute effects are shown in ellipses, and subacute and longer term therapeutic consequences are shown in rectangles in either the vascular smooth muscle or pulmonary endothelial target tissues: PGI2, or prostacyclin, is a natural PEC product that relaxes SMC via increases in intracellular cAMP levels. Inhibitors of type 3 phosphodiesterases (PDE3), such as milrinone, stabilize the cAMP concentration; PEC also produce the gasotransmitter nitric oxide (NO) which dilates SMC by boosting cGMP levels, and these levels are buttressed by the PDE5 inhibitors, including sildenafil; The third class of PEC products that has inspired pharmacotherapy for PH is the endothelin receptor blocker group. ET-1 is a vasoconstrictor that is produced by PEC and broad-spectrum blockers of both ET_A- and ET_B-type receptors, such as bosentan, decrease SMC tone. Figure concept after Humbert et al.[86]

TABLE 1

Future Directions and Gaps in Knowledge

Burden of disease	
1	To quantify the incidence of PH among preterm infants
2	To understand the natural history and outcomes of PH in preterm infants by large prospective multi-center studies in different areas of the world
3	To understand the economic impact of PH on the families of preterm infants and society
4	To understand the impact of PH on quality of life in preterm infants and their families
Risk factors for disease	
1	To identify in utero factors or conditions that increase risk of PH in preterm infants
2	To identify postnatal risk factors that increase risk of PH in preterm infants
3	To identify risk factors that may exacerbate or cause recurrent PH in preterm infants, including viral infections, lower respiratory tract disease, upper airway obstruction, intermittent hypoxia and hypercarbia, feeding problems with aspiration, and gastro-esophageal reflux
Pathophysiology of disease	
1	To identify and classify subtypes of PH within preterm infants
2	To understand the developmental aspects of specific molecular pathways in the preterm pulmonary vasculature that may influence development of PH
3	To understand the integrative control of pulmonary microvascular development and remodeling by genetic and environmental factors, and the impact of these issues on the number, lumen size, and reactivity of pulmonary resistance vessels
4	To identify the genetic and epigenetic factors that influence the development and severity of PH
Diagnosis of disease	
1	To identify and validate serum biomarkers for diagnosis and tracking disease severity of PH
2	To determine and optimize the best non-invasive studies for PH diagnosis in preterm infants
3	To develop criteria for the diagnosis for preterm infants, including the use of data from echocardiograms and cardiac catheterization
Management of disease	
1	To develop guidelines for treatment and preventative strategies for preterm infants at risk for PH
2	To understand the risk of anesthesia in preterm infants with PH and to develop strategies to limit complications and optimize outcomes
3	To understand the role of existing PH medications in preterm infants with PH
4	To determine optimal stabilization and treatment strategies in the emergency department and intensive care unit
5	To measure the role of newer therapeutic strategies including the inhibition of rho-kinase and arginase II in acute and long-term PH management