Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia

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Owing to antenatal steroid use, surfactant therapy, improved ventilator care, better nutrition, and other interventions, survival of extremely low gestational age newborns has markedly increased over the past decades.[1-5] With this improved survival, however, the incidence of bronchopulmonary dysplasia (BPD), the chronic lung disease that follows respiratory support after preterm birth, has tended to increase.[5-7] Controversies regarding a formal definition of BPD persist; however, BPD is generally defined by the requirement for supplemental oxygen at 36 weeks' postconceptual age in infants born at or below 32 weeks' gestation as based on workshop recommendations from a National Institutes of Health workshop in 2001.[1] Recent work suggests that early evidence of pulmonary vascular disease is associated with development of BPD,[8,9] and pulmonary hypertension (PH) continues to be strongly associated with the severity of BPD, and poor outcomes.[5,10-18] Unfortunately, high-quality evidence on which to base the care for infants with BPD-associated PH (BPD-PH), and consensus care guidelines are generally lacking, and marked differences exist, even among experienced centers, regarding optimal approaches for the diagnosis, evaluation, and management of BPD-PH.

A joint report from the American Heart Association and the American Thoracic Society recently presented the first guidelines for the care of children with diverse causes of PH.[6] Although work from this group included formal grading of recommendations regarding the care of infants with BPD-PH, many important issues specifically related to preterm infants with BPD were not addressed in detail as they were not within the scope of the project.[6]

To address the need for detailed recommendations, this report presents consensus recommendations for the care of children with BPD-PH as developed by the Pediatric Pulmonary Hypertension Network (PPHNet), an interactive, multidisciplinary group of PH experts from 10 North American PH programs.[19] Specifically, the approach to the evaluation, management, and follow-up of infants with BPD who are at risk for or diagnosed with PH is presented, while acknowledging limitations in current data and identifying key knowledge gaps requiring further study.

ASDs	Atrial septal defects
AVT	Acute vasodilator testing
BPD	Bronchopulmonary dysplasia
BNP	Brain natriuretic peptide
CCB	Calcium channel blockers
CT	Computed tomography
FiO_2	Fraction of inspired oxygen concentration
iNO	Inhaled nitric oxide
LOE	Level of evidence
LV	Left ventricular
NICU	Neonatal intensive care unit
NT-proBNP	N-terminal-probrain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
PMA	Postmenstrual age
PPHN	Persistent pulmonary hypertension of the newborn
PPHNet	Pediatric Pulmonary Hypertension Network
PVR	Pulmonary vascular resistance
PVS	Pulmonary vein stenosis
RV	Right ventricular
sPAP	Systolic pulmonary artery pressure
TRJV	Tricuspid regurgitant jet

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Methods

A working group from PPHNet specialists that included neonatologists, cardiologists, pulmonologists, and intensivists was established to create this document. Although recognizing the lack of randomized multicenter trial data for many questions, the goal was to establish practical clinical recommendations for the evaluation, diagnosis and management of PH in infants with BPD based on extensive review of currently available publications in combination with expert opinion. This document further describes clinical strategies for the diagnosis, evaluation, and therapy of PH in infants with BPD to assist healthcare providers in clinical decision making. Members of PPHNet completed surveys and participated in teleconference calls to help identify critical questions for discussion by the working group and to make consensus recommendations.

In general, class of recommendation (class), an estimate of the size of effect, was considered by balancing known risks vs benefits, with class I denoting stronger evidence than class II for benefit over risk and class III referring to interventions that are of no benefit or potential harm to the patient. The level of evidence (LOE), an estimate of the precision of the treatment effect as designated by A, B, or C, was based on the working group's ranking of strength of evidence supporting each recommendation, according to the quality of available data. Evidence was ranked as level C when the primary strength of the recommendation was based on expert opinion, case studies, or general standards of care, which was true for most of the clinical issues addressed in this report. Because randomized clinical trials are lacking on many aspects of the topic, much of the available data are from small case series or reports, including studies from other relevant pediatric PH populations, and most of these recommendations are based on expert consensus (level C). The levels of evidence and strength of recommendation noted throughout the document were established based on group adjudication of individual scoring by the working group members. Although these recommendations attempt to define best practices to meet the needs of most patients, decisions about the care of any specific patient must be made by the practitioner with careful consideration of the individual circumstances present for the given patient and family. Our recommendations are summarized in **Table I** (available at www.jpeds.com).

General Recommendations

Recommendation # 1: A multidisciplinary team of neonatologists, pulmonologists, cardiologists, intensivists, and PH specialists, should be involved in the care of infants with BPD-PH to ensure a comprehensive and consistent approach. (class I, LOE C)

Rationale: Recommendations for multidisciplinary care are based on the complex pathophysiology of PH in BPD, which can be strongly associated with several contributing factors, including critical heart-lung interactions, the presence of anatomic cardiac shunt lesions, structural airways disease, lung inflammation, airways hyper-reactivity, and chronic aspiration among others, as recently highlighted.[20,21] Because PH in BPD is associated with significant morbidity and mortality, management of PH should be guided by PH specialists from diverse backgrounds who are experienced in the care of infants and children with PH.[19] The roles of experienced neonatal intensive care unit (NICU) nurses and respiratory therapists are extremely important in the management of these infants. Rapidly expanding experience with PH-specific drug therapies, cardiac imaging, approaches to the evaluation of factors that contribute to the severity of the underlying lung disease, and other factors suggest strong benefits from interdisciplinary care. Multiple clinical problems associated with prematurity, such as necrotizing enterocolitis, recurrent infections and neurologic issues can complicate the course of an infant's NICU stay. Expert management is necessary to understand how treating each of these systems could help improve clinical outcomes. Similarly, a multispecialty team likely enhances long-term management of these children that links inpatient and ambulatory care post-NICU discharge. Early involvement of the teams providing long-term care provides not only improved communication and consistent treatment planning, but excellent continuity for the patient, family, and providers.

Evaluation and Diagnosis

Recommendation # 2: Premature infants should have an echocardiogram performed to screen for PH in the following scenarios:

(1) *severe hypoxemic respiratory failure shortly after birth attributed primarily to persistent pulmonary hypertension of the newborn (PPHN) physiology despite optimal management of underlying lung disease. (class 1, LOE B)*
(2) *continued need for ventilator support at postnatal day 7, as echocardiogram evidence of PH at day 7 suggests high risk for BPD and may alter therapy. (class1, LOE C)*
(3) *with sustained need for significant respiratory support at any age, especially with recurrent episodes of hypoxemia. (class 1, LOE B)*
(4) *at the time of formal BPD diagnosis per current practice (36 weeks postmenstrual age [PMA]). (class 1, LOE B)*

Rationale: At birth, the pulmonary circulation undergoes striking adaptive changes, including a fall in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), which leads to a rapid and marked rise in pulmonary blood flow. Although preterm newborns undergo similar changes as term infants during this transition, little data exist that examines the rate of these physiologic changes after preterm birth and the impact of variable degrees of lung disease. As a result, defining PH during first days of life is incompletely understood. The value of echocardiography for assessing PH and congenital heart disease in the newborn is well-established; however, the timing and frequency for echocardiograms in preterm infants for the evaluation of PH is highly variable among centers, but should be strongly considered in the above scenarios. Preterm infants with severe hypoxemic respiratory failure, especially in the setting of oligohydramnios and intrauterine growth restriction, are more likely to have abnormalities in pulmonary vascular tone and reactivity, and are at risk for extra-pulmonary

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shunting across the ductus arteriosus and/or foramen ovale because of PPHN physiology.[22-25] The documentation of PPHN physiology, although excluding significant congenital heart disease, is important for clinical decision making.

Although studies have shown the use of inhaled nitric oxide (iNO) in preterm infants as not beneficial in reducing the incidence of BPD, these studies did not examine the potential role of iNO for the treatment of (PPHN) in the preterm. iNO in the setting of echocardiographic evidence of right-to-left extrapulmonary shunting can acutely improve oxygenation and hemodynamics, particularly when parenchymal lung disease does not appear to be severe.[6,26,27] Several case series have demonstrated that iNO can improve oxygenation and hemodynamics in severe respiratory failure in preterm infants, especially with oligohydramnios and prolonged premature rupture of membranes, in the presence of PPHN physiology.

Prospective studies in preterm infants have suggested that a diagnosis of PH as early as postnatal day 7 is strongly associated with a high risk for subsequent development of BPD at 36 weeks PMA, suggesting a close relationship between angiogenesis and alveolar growth.[9,13,28] These early signs of pulmonary vascular disease may provide an early biomarker for disease risk, and potentially a change in BPD and/or PH management. No studies to date, however, have examined whether early PH therapy in these infants impacts late outcomes.

Finally, regardless of whether initial studies are negative for PH, an echo should be repeated if an infant develops increasing oxygen or respiratory support requirements either during the initial or subsequent hospitalizations, as PH may develop despite having a normal echocardiogram at discharge (**Figure**). Older infants can develop late PH during acute viral respiratory infections or may present with nonspecific findings including worsening feeding difficulties, poor weight gain, increasing oxygen requirements, and/or escalating respiratory support at home or in the hospital.[20] As several studies have reported a 15%-25% incidence of PH in preterm infants with severe BPD, echocardiograms should be routinely performed in preterm infants meeting clinical criteria for BPD at 36 weeks' PMA, especially with high fraction of inspired oxygen concentration (FiO_2) requirements or prolonged ventilator support.[9,18,29] Persistently elevated $PaCO_2$ as a marker of the underlying severity of the lung disease or problems with control of breathing may also be an indication for repeat PH screening. If echocardiogram screening demonstrates PH, follow-up studies should initially be performed frequently (1-2 weeks) to monitor response to interventions, and then repeated less frequently (eg, monthly) while still hospitalized as the infant becomes more stable; (ie, the frequency of follow-up studies should be dictated by clinical course) (**Figure**).

Recommendation 3: A complete echocardiogram for PH screening in preterm infants should include, at a minimum: (1) a complete anatomic evaluation, to identify and characterize the physiologic contribution of structural abnormalities, shunts and pulmonary veins; (2) assessment of right and left ventricular size, hypertrophy, systolic, and diastolic function; (3) systolic and diastolic interventricular septal position; (4) tricuspid and pulmonary regurgitation jet velocities (when present); (5) simultaneous systemic blood pressure documentation. (class 1, LOE B)

Rationale: Estimated systolic pulmonary artery pressure (sPAP) as derived from the tricuspid regurgitant jet (TRJV) measured by echo has become one of the most utilized clinical tools for evaluating PH. The peak pulmonary regurgitant velocity also gives a rough estimate of the mean PAP (**Table II**). However, many infants do not have enough TR for accurate and reproducible measurements of TRJV by Doppler evaluation and the value may not be a reliable estimate of right ventricular (RV) pressures.[29] In addition, factors associated with chronic lung disease, including lung hyperinflation and altered position of the heart, can adversely affect the ability to detect and measure TRJV. Past studies have shown excellent correlation coefficients for sPAP when measured during cardiac catheterization (cath) in children less than 2 years of age with congenital heart disease.[30] When the utility and accuracy of echo for predicting disease severity was studied in preterm infants with BPD in whom echos were followed by cardiac catheterization days to weeks later, correlations of estimated sPAP were less consistent. Specifically, sPAP could be estimated by echo in only 61% of studies, and there was poor correlation between echo and cath measures in these infants.[31] These differences likely reflect, in large part, the different conditions under which the studies were performed; ie, echocardiograms are generally performed while awake whereas catheterization studies are often performed during mechanical ventilation with anesthesia or sedation. Additionally, cath measurements may reflect the effects of acute changes in lung volume, gas exchange, and systemic hemodynamics during ventilation with anesthesia.

As used in clinical practice, however, echocardiography is reasonably sensitive for detection of PH in infants with BPD, and the use of multiple markers of elevated right ventricular pressure, such as septal flattening, RV dilation and/or hypertrophy, and depressed function, even in the absence of a reliable TR by Doppler in infants with BPD are strongly supportive of PH but not necessarily accurate regarding disease severity (**Table II**). Along with the complete assessment of RV performance, equally careful assessment of left ventricular (LV) systolic and diastolic function is important in determining the etiology of PH and to guide therapy.

Pulmonary vein stenosis (PVS) has been reported with growing frequency in the BPD population and is associated with high mortality.[32,33] In a Spanish registry study, PVS was identified in 26% of subjects with BPD-PH selected to undergo cardiac catheterization.[33] In patients with severe BPD-PH, pulmonary vein flow and gradients should be examined as part of each study, as PVS may become apparent over time despite negative initial studies, especially in infants with a history of necrotizing enterocolitis.[34,35] Pulsed Doppler interrogation of all pulmonary veins, especially left sided veins, is recommended, and continuous, nonphasic flow, or absence of late diastolic flow reversal in the presence of nonphasic flow, suggests PVS even in the setting of low mean gradients.[36] If pulmonary vein assessment is incomplete or inconclusive by echo, or if PVS is diagnosed in the setting of PH, cardiac catheterization, computed tomography (CT) angiography, or

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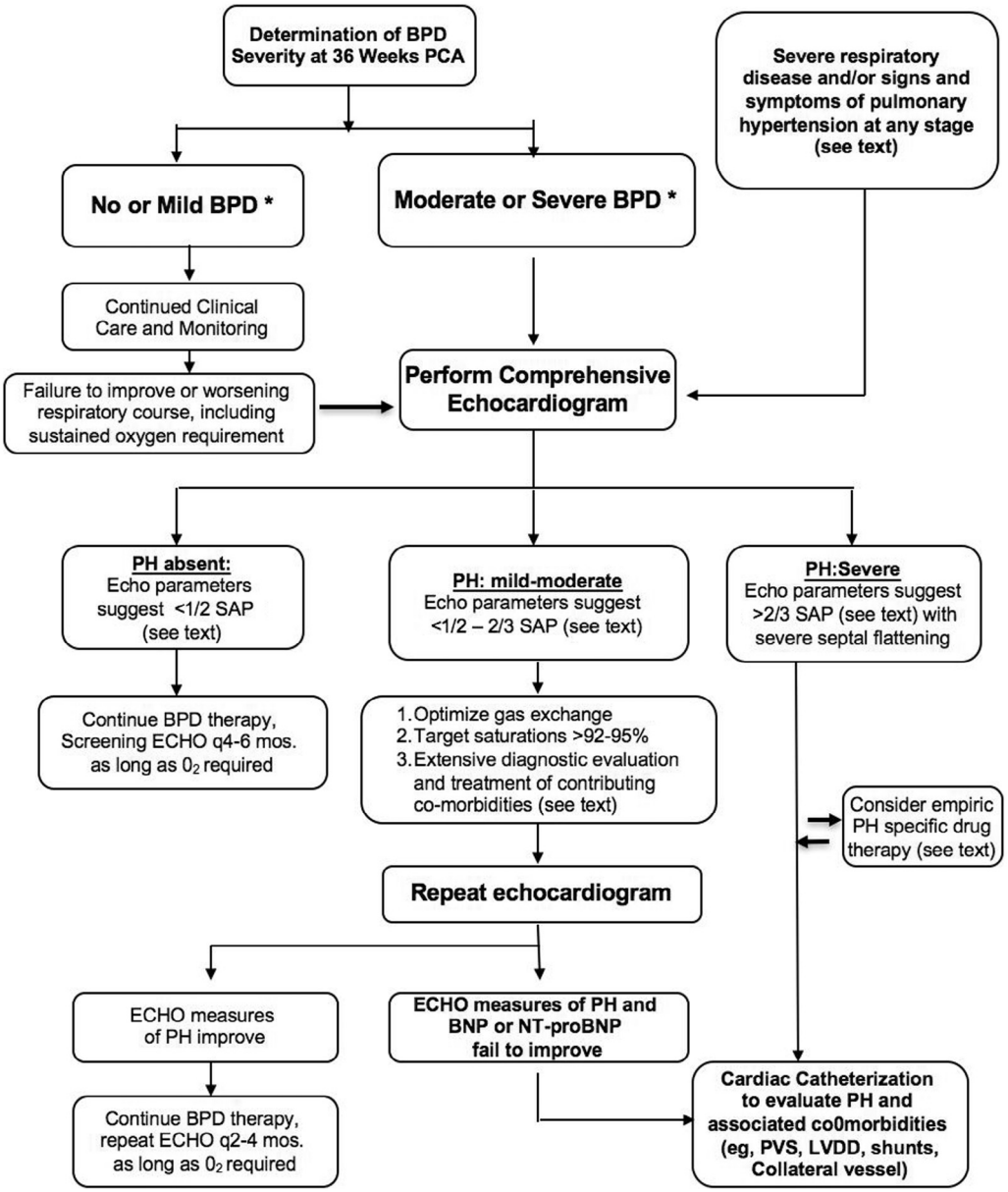

Figure. Clinical approach for the evaluation and treatment of PH in BPD infants. *ECHO*, echocardiogram; *LVDD*, LV diastolic dysfunction; *O_2*, oxygen; *SAP*, systemic arterial pressure.

magnetic resonance imaging should be performed to comprehensively evaluate the impact of PVS.[33,36-38] In a recent retrospective review, a median of 5 echocardiograms were performed prior to a diagnosis of PVS, suggesting that PVS may develop or progress late in the clinical course.[34] PVS in premature infants with BPD may occur late after discharge from the NICU and continued surveillance and repeat echocardiography is important, especially in infants who demonstrate signs of worsening PH or an inability to wean oxygen support.

A complete echo should include evaluation of intracardiac and arterial shunts and clearly define pressure gradients and the net direction of flow. The presence of "low velocity" flow or right to left shunting across a ductus, for example, indicates severe PH. Echocardiograms may provide evidence of left ventricular diastolic dysfunction that may contribute to PH or recurrent pulmonary edema, but may not be sufficiently sensitive to exclude its presence. In the setting of high diuretic requirements for recurrent or persistent pulmonary edema or in the setting of poor responsiveness to PH-specific therapy, echo-based markers of left ventricular diastolic dysfunction should be specifically evaluated (**Table II**).[39-41] As echocardiography may not be sufficient for making the diagnosis of left ventricular diastolic dysfunction, cardiac catheterization or other imaging approaches may be needed for further evaluation.

Recommendation # 4: When diagnostic studies are consistent with PH, baseline and serial brain natriuretic peptide (BNP)

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Table II. Echocardiographic assessment of pulmonary hypertension in preterm infants with BPD

Recommended measurements for each study

Echo measurements	Views	Information	Comments
Standard measures:			
RV size and RVH	PSAX, Apical 4 chamber	Multiple views	Qualitative measure
IVS position	PSAX; subcostal and apical 4 chamber views	Indirect estimation of RVSP	Flat, ~ 1/2 systemic RVSP; Flat-Posterior systolic bowing – systemic RVSP; severe posterior systolic bowing-LV pancaking- suprasystemic RVSP
RV function	PSAX, subcostal	RV systolic function	Qualitative measure (not very accurate)
TRJV	Ap4CH, PSAX, PLAX	Estimate RV systolic pressures using the Bernoulli equation. $RVSP = 4TRJV^2$	TR may not be always present even with PH and TRJV may be inconsistent for reliable quantification
PR gradient	RV outflow Doppler PSAX	Estimate mean and end diastolic PA pressures	Useful adjunct to TR gradient
Shunt gradient (VSD or PDA)	All views obtained with adequate Doppler alignment	Estimate RV and PA systolic pressures and physiologic role	Useful to assess RV pressures and potential contribution of shunt to PH
LV size and LVH, systolic and diastolic function	M-Mode, PSAX, Ap4CH, Doppler, tissue Doppler	Assess LV measurement	Important in severe PH with septal flattening or systemic hypertension
Pericardial effusion	Subcostal, PSAX, Ap4CH	Document presence and size	Associated with severe PH
Additional measurements of PH			
TAPSE	Ap 4CH- M-Mode or 2D Echo	Useful RV measurement for PH and longitudinal contractility	correlates with S' on tissue Doppler (mention utility of metric here)
RVFAC	Ap 4CH	Derived from planimetric areas of the RV in systole and diastole	Quantitative measure- requires good visualization of the RV walls
RV/LV ratios during systole and diastole	Ap 4CH and PSAX	RV/LV ratio and LV eccentricity index, a marker of dysfunction	LV eccentricity index is LV end systolic dimension parallel and perpendicular to the septum.
RVOT Doppler profile	PSAX, Ap4CH	Midsystolic notch correlates with PVR	Absent notch in established PH suggests pulmonary venous hypertension (79,80)
Tissue Doppler indices for RV and LV function	Ap 4 CH at mitral, septal and tricuspid valve annulus	LV and RV Diastolic function- E/E'; S'; E'/A'	Measure of LV and RV diastolic function
Tei index (by inflow Doppler)	Ap 4Ch- Tricuspid and mitral inflow Doppler	Systolic and diastolic Function	
RV MPI (tissue Doppler)	Ap 4CH	RV systolic and diastolic function	RV MPI is estimated from tricuspid valve inflow Tissue Doppler images. The time from cessation to the beginning of tricuspid inflow (a) and RV ejection time (b) are measured. RV MPI = (isovolumic contraction time + isovolumic relaxation time) / ejection time = (a - b) / b

Ap 4CH, apical 4-chamber; *IVS*, interventricular septum; *MPI*, myocardial performance index; *PA*, pulmonary artery; *PLAX*, parasternal long axis; *PR*, pulmonary regurgitation; *PSAX*, parasternal short axis; *PV*, pulmonary vein; *RA*, right atrium; *RVH*, right ventricular hypertrophy; *RVSP*, RV systolic pressure; *TAPSE*, tricuspid annular plane systolic excursion; *VSD*, ventricular septal defect.

or NT-pro-BNP measurements may assist in the assessment of cardiac performance. These tests may augment clinical decision making but do not replace the use of echocardiogram or cardiac catheterization for PH assessment. (class 1, LOE B)

Rationale: Serum BNP and N-terminal-probrain natriuretic peptide (NT-proBNP), which are released by the myocardium in response to stretch, are used as biomarkers for monitoring changes in disease status in children with known PH, but are not specific for RV stress or PH per se. Several studies have correlated BNP and NT-proBNP levels with BPD severity, presence of a patent ductus arteriosus (PDA), and other outcomes.[42,43] Serial BNP or NT-proBNP levels may be useful in monitoring disease progression/regression, response to therapy, and in modulating decision making, but these biomarkers should be used in conjunction with echo rather than in isolation, though they may decrease the overall number of echocardiograms performed.

Recommendation #5: Further evaluation and treatment of comorbidities that impact the severity of lung disease should be undertaken with the diagnosis of BPD-PH infants before the initiation of pulmonary arterial hypertension (PAH)-targeted therapy. Studies should include evaluation for intermittent or sustained hypoxemia, aspiration, gastroesophageal reflux disease, structural airways disease, pulmonary artery and vein stenosis, left ventricular diastolic dysfunction, and aortopulmonary collaterals. (class 1, LOE B)

Rationale: Management of BPD-PH begins with treating the underlying lung disease. This approach generally includes an extensive evaluation for chronic reflux and aspiration, structural airway abnormalities (such as vocal cord paralysis, subglottic stenosis, tracheomalacia, and other lesions), assessment of bronchial hyper-reactivity, reduction of lung edema, mucus clearance, and optimization of ventilator care.[20] Chronic or intermittent hypoxia is a common cause of late presentation of PH or the failure of PH to resolve in infants with BPD. Brief assessments of oxygenation ("spot checks") are not sufficient for making decisions regarding the level of supplemental oxygen therapy. Use of pre- and postductal oxygen saturation monitoring in infants with an open ductus arteriosus is useful in estimating for significantly elevated pulmonary artery pressures, especially during an apparent PH crisis. Targeting oxygen saturations to 92%-95% should be sufficient to prevent the adverse effects of hypoxia in most infants, without increasing the risk of additional lung injury or oxygen damage. Home pulse oximetry studies during sleep or a formal sleep study may be helpful to determine the presence of significant episodes

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Table III. Echocardiogram findings of pulmonary hypertension and its severity

None: RVSP <1/3 systemic pressure by TR gradient; septal position rounded and committed to LV; no RVH; normal RV size and function; If present, large VSD or PDA gradients suggesting <1/3 systemic RV pressures (Ao pressure – gradient = PA pressure)
Mild: RVSP 1/3-1/2 systemic pressure; septal flattening in systole, mild RVH and RV dilatation, RV function may be normal.*
Moderate: RVSP ½-2/3 systemic pressure; septum flat or with late systolic posterior bowing, moderate RVH or dilatation, RV may have reduced function*.
Severe: RVSP >2/3 systemic pressure; If present, shunt with predominant R-L gradient, pansystolic posterior septal bowing, Severe RVH, RV dysfunction, RV dilatation, "low-velocity" shunting across PDA or VSD.*

Dilated right atrium, right to left atrial shunt, posterior bowing of the atrial septum, dilated inferior vena cava and dilated coronary sinus are also evidence of RA hypertension and RV diastolic dysfunction.
*RV size, hypertrophy, and function will depend on the duration of PH and should not be used as measures of RV pressures, but as supportive evidence.

of hypoxia, which may lead to the worsening or persistence of PH, and to characterize the impact of obstructive or central apnea. Sleep patterns are frequently abnormal in BPD; however, infant norms for polysomnography are generally lacking and the study may be difficult to perform in a NICU setting. Prolonged oxygen saturation monitoring during sleep is often used in the outpatient setting to guide weaning from supplemental oxygen.

Additional studies to identify causes of persistent lung disease often include flexible bronchoscopy for the diagnosis of anatomical and dynamic airway lesions (such as tracheomalacia, bronchomalacia, airway stenosis, and granulomas) that may contribute to hypoxemia and poor clinical responses to oxygen therapy. An upper gastrointestinal series, pH or impedance probe, and swallow studies may be indicated to detect gastroesophageal reflux and aspiration, potential contributors to ongoing lung injury. Selected patients may benefit from the administration of jejunal feedings or fundoplication to avoid aspiration complicating the severity of lung disease. For selected patients with BPD and PH with severe lung disease, especially with chronic respiratory distress, recurrent cyanotic episodes, or high FiO_2 requirements, consideration should be given to chronic noninvasive or invasive assisted mechanical ventilation to provide adequate levels of respiratory support. Infants who have severe BPD inconsistent with their degree of prematurity (eg, ≥29 weeks gestational age) should have genetic studies, lung CT scan, and possible lung biopsy to evaluate the potential diagnosis of developmental lung diseases (such as alveolar capillary dysplasia, surfactant protein deficiencies, pulmonary lymphangiectasia, and pulmonary interstitial glycogenosis).[44]

Recommendation #6: In selected cases, cardiac catheterization should be performed to: (1) confirm the echocardiographic diagnosis of PH, (2) determine disease severity, (3) evaluate the potential contributions of shunt lesions (atrial septal defect [ASD], PDA, or VSD), PVS, LV diastolic dysfunction, aortopulmonary collaterals, and close shunts if appropriate, (4) to define the need for the addition of combination drug therapy, especially systemic prostanoid therapy, and (5) prior to the addition of combination drug therapy, especially systemic prostanoid therapy, in the setting of clinical deterioration and echocardiographic evidence of increasing PH or decreasing ventricular function. (class 1, LOE B)

Rationale: Currently, many preterm infants with PH who are diagnosed by echocardiogram are initially treated with a PH-specific drug without cardiac catheterization. The decision to perform a cardiac catheterization should be carefully considered, especially in very small infants and those on high levels of ventilator support because of the risk for significant vascular and hemodynamic complications in this group. In addition, marked differences can exist regarding the level of experience in performing cardiac catheterization in sick preterm infants, and cardiac catheterization should not be performed without a team equipped with handling pulmonary hypertensive emergencies in sick infants.[45-47] As such, we suggest that cardiac catheterization should be considered prior to initiation of therapy but may be delayed at the discretion of the care team and that this decision should be based on balancing the need to obtain critical hemodynamic information that may significantly determine interventions and clinical management with the potential risks of the procedure. In patients without associated structural heart disease, the goals of cardiac catheterization are to assess the severity of PH, pulmonary venous desaturation (as an indicator for severity of lung disease), rule out pulmonary venous obstruction and systemic-pulmonary collateral vessels, and assess pulmonary vascular reactivity (**Table III**). Acute vasodilator testing (AVT) should be performed to determine the response to oxygen (as a potential therapy) and/or inhaled nitric oxide to assist with risk stratification, and determination of the physiologic impact of oxygen and vasodilator therapy, especially in the setting of shunt lesions or LV dysfunction.[48,49] In contrast with the use of AVT to guide the potential use of calcium channel blocker therapy in older patients with PAH,[6] a positive AVT response in infants with BPD should not be considered as an indicator for calcium channel blocker therapy, and lack of response does not preclude the use of PH-specific drug therapy.

In preterm infants with associated congenital heart disease, accurate physiological assessment of shunt lesions and determination of PVR are critical. The management of left-to-right shunt lesions including ASDs and PDA must be considered carefully in infants with BPD-PH. Generally, a prior period of clinical stability and the lack of right-to-left ductal shunting by monitoring pre- and postductal saturations in the NICU may indicate that the PDA should be considered for possible closure. However, these patients should undergo meticulous hemodynamic assessment in the cardiac catheterization laboratory prior to consideration of closure. Some patients with shunts may require additional evaluation by testing the hemodynamic effects of temporary occlusion of the lesion during cardiac catheterization. Patients with elevated PAP and/or right-to-left shunting may require treatment for a period of time

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with PH-specific drug therapy prior to repeat hemodynamic assessment. It is important to note that elimination of a significant left-to-right shunt can result in resolution of significant PH when there is little pulmonary vascular disease per se. However, the closure of the ASD or PDA may be dangerous in the presence of significant pulmonary vascular disease because such lesions are needed as a "pop off" to relieve right ventricular pressure and sustain cardiac output at times when critical elevation could be dangerous for the infant.[47,50] Hemodynamic indications and guidelines for closure are outside the spectrum of this review but are described elsewhere.[6]

Angiography to evaluate the presence, size, and significance of bronchial or systemic collateral arteries and pulmonary vein anatomy may provide insight into other contributors of elevated pulmonary artery pressures. Elevated pulmonary capillary wedge or left atrial pressures represent left ventricular diastolic dysfunction, which has been described in up to 25% of catheterization studies in BPD.[40,43,47,51] This should be clinically suspected in infants with BPD and recurrent pulmonary edema, and/or poor iNO responsiveness. Some infants with left ventricular diastolic dysfunction present with persistent requirements for frequent diuretic therapy to treat recurrent pulmonary edema, even in the presence of only mild PH. Use of afterload reducing drugs (such as milrinone and angiotensin converting enzyme inhibitors), and diuretics may improve symptoms and lung function in such infants.[37,39] Findings supporting a diagnosis of left ventricular diastolic dysfunction are sometimes masked by decreased intravascular volume because of chronic diuretic use, in particular with systemic hypotension that occurs during anesthesia. In selected cases, administration of a small fluid bolus at the time of catheterization may increase pulmonary wedge pressures, unmasking left atrial hypertension associated with left ventricular diastolic dysfunction.

CT angiography in high risk infants may be a procedure of initial choice to evaluate PVS, aortopulmonary collaterals and parenchymal lung disease[33] and may be performed prior to cath. Transcatheter closure of aortopulmonary and atrial shunts have been described in this age group, and consideration should be given to surgical closure in small infants if appropriate.[51-54] Noting risks of vascular injury in very small infants, the choice of transcatheter vs surgical closure should be based on the condition and size of the patient as well as institutional and operator experience.[53] Transcatheter or surgical intervention of significant pulmonary vein stenosis in this setting has only limited success and is usually associated with progressive worsening and increased mortality.[55,56]

Therapeutic Strategies and Follow-up:

Recommendation # 7: Supplemental oxygen therapy should be used to avoid episodic or sustained hypoxemia and with the goal of maintaining oxygen (O_2) saturations between 92%-95% in patients with established BPD and PH. (class 1, LOE B)

Rationale: To avoid intermittent or chronic hypoxemia that can increase the severity or delay resolution of PH, it is important to maintain oxygen saturations in the 92%-95% range in infants with established BPD and PH. Even mild degrees of oxygen desaturation can markedly elevate pulmonary artery pressure in BPD infants with PH.[49,53,57-61] Prior to the availability of PH-specific drug therapy, chronic supplemental oxygen therapy with close monitoring was associated with resolution of PH in many cases, along with enhanced growth and neurocognitive outcomes. Overzealous use of high levels of oxygen by targeting oxygen saturations beyond the recommended range, however, may theoretically contribute to airway inflammation and should be avoided.[5,62] Acute viral respiratory infections can lead to striking increases in PH and coincide with the need for higher FiO_2 and increased respiratory support.[7,20] Serial assessments of chronic oxygenation with home pulse oximetry studies, especially during sleep, inpatient polysomnography, and related pulmonary evaluations are recommended to help guide outpatient oxygen weaning.

Recommendation # 8: iNO should be used for acute PH crises and weaned after stabilization. (class I, LOE B) The addition of sildenafil therapy may be helpful in weaning from nitric oxide. (class IIa, LOE B)

Rationale: Infants with BPD can have progressive worsening of PH or acute elevations of PAP because of viral infections with parenchymal inflammation or hypoxia triggering acute deterioration. These infants often present with sudden lability in their saturations with profound desaturations and hypotension in response to even simple daily care interventions. An initial evaluation to rule out airway obstruction and acute atelectasis or pneumonia should be performed before considering escalation of PH therapy. These acute episodes may necessitate escalation of ventilator support, measures to treat the offending trigger (eg, antibiotics for infection, steroids for inflammation, gastroesophageal reflux therapy), and PH-directed therapies and inotropes to support cardiac function. iNO causes selective pulmonary vasodilation and improves oxygenation in infants with established BPD.[5,49,63] A dose of 10-20 PPM should be used for acute PH crises and weaned after stabilization as tolerated.[24,49] Low dose iNO may further improve ventilation-perfusion matching, allowing for better oxygenation at lower FiO_2, whereas higher doses (20 ppm) favor improvements in pulmonary hemodynamics. Weaning strategies vary and usually involve initial rapid weaning to a dose of 3-5 PPM, followed by a more gradual reduction by 1 PPM before being stopped. The need for increasing FiO_2 or echo evidence of worsening PH suggests the need for reinitiation of iNO. By prolonging cGMP levels during iNO induced vasodilation, PDE-5 inhibitors may be useful to augment the response to iNO therapy or to prevent rebound PH after abrupt withdrawal of iNO.[64,65] Although both therapies are expensive, the transient use of sildenafil may prevent the reinstitution of iNO and provide an overall cost savings.

Recommendation # 9: PH-targeted therapy should be considered for infants with BPD and sustained PH after optimal treatment of underlying respiratory and cardiac disease. (class I, LOE B) Pharmacologic therapy should be initiated in patients with evidence of significantly elevated pulmonary vascular resistance and right ventricular impairment (moderate hypertrophy or dysfunction) not related to left heart disease or pulmonary vein stenosis. (class I, LOE B) (**Table IV**)

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Table IV. Pharmacotherapy of pulmonary hypertension in BPD

Names	Dose/titration	Side effects	Comments
Sildenafil phiosphodiesterase-5 inhibitor	PO: 1 mg/kg 6-8 h; start with low dose (0.3-0.5 mg/kg/dose) and increase gradually to 1 mg/kg/dose as tolerated; slower as outpatient. Maximal dose of 10 mg q 8 h per EMA guidelines for infants. Intravenous:0.25-0.5 mg/kg/dose q 6-8 h (titrate slowly and administer over 60 min.	Hypotension, GER, irritability (headache), bronchospasm, nasal stuffiness, fever, rarely priapism	Monitor for adverse effects, lower the dose or switch to alternate therapy if not tolerated
Bosentan (Endothelin receptor antagonist)	1 mg/kg PO q 12 h as starting dose; may increase to 2 mg/kg BID in 2-4 wk, if tolerated and liver enzymes stable.	Liver dysfunction especially during viral infections, VQ mismatch, hypotension, anemia (edema and airway issues rare in infants)	Monitor LFTs monthly (earlier with respiratory infections); monitor CBC quarterly. Teratogenicity precautions for caregivers
Inhaled Iloprost	2.5-5 mcg every 2-4 h. Can be given as continuous inhalation during mechanical ventilation. Can titrate dose from 1-5 mcg and frequency from every 4 h to continuous.	Bronchospasm, hypotension, ventilator tube crystallization and clogging, pulmonary hemorrhage, prostanoid side effects (GI disturbances), may be teratogenic to caregivers	Need close monitoring for clogged tubing, may need further dilution. May need bronchodilators or inhaled steroid pretreatment with bronchospasm.
Intravenous Epoprostenol (Flolan)	Start at 1-2 ng/kg/min, titrate up slowly every 4-6 h to 20 ng/kg/min; need to increase dose at regular intervals because of tachyphylaxis. Further increases as guided by clinical targets and avoiding adverse effects.	Hypotension, VQ mismatch, GI disturbances. Needs dedicated line, very short half-life with high risk for rebound PH with brief interruption of therapy; line related complications include infection, clogging, breaks in line, thrombosis, arrhythmia)	Monitor closely if added to other vasodilator therapies, such as milrinone; careful attention to line care is essential.
Treprostinil (Remodulin) IV or Subcutaneous	Start at 2 ng/kg/min and titrate every 4-6 h up to 20 ng/kg/min, then slow increase dose as tolerated (dose often 1.5-2 times greater than equivalent epoprostenol dose, if switching medications)	SQ: local site pain; IV: similar risks as with epoprostenol, but treprostinil has a longer half- life, which reduces risk for severe PH with interruption of infusion	Site pain managed with local and systemic measures
Milrinone (IV) (phosphodiesterase-3 inhibitor)	0.15-0.5 mcg/kg/min –lower dosage range when used with other vasodilators	Arrhythmogenic; systemic hypotension and high risk for decreased myocardial perfusion; caution with renal dysfunction	May need to add a pressor, such as vasopressin, to mitigate effects of decrease in systemic pressures.

BID, twice a day; *CBC*, complete blood count; *EMA*, European Medicines Agency; *GER*, gastroesophageal reflux; *GI*, gastrointestinal; *IV*, intravenous; *kg*, kilogram; *LFT*, liver function tests; *mcg*, microgram; *ng*, nanogram; *PO*, oral; *SC*, subcutaneous; *SR*, sustained release; *VQ*, ventilation-perfusion.

Recommendation #10: Decisions regarding selection, initiation, and modification of PH-specific therapy should be made based on disease severity, drug tolerance (and availability/cost), and in consultation with PH specialists. (class I, LOE C)

Rationale: Despite the availability of PH-specific drugs for the treatment of PH, there remain many controversies regarding the use of these agents in BPD.[6,64,66] There are limited data demonstrating efficacy in infants with BPD; hence, the guidance of a team that includes PH specialists with experience in the management of treated infants is encouraged, and the use of PH-specific drugs should follow thorough diagnostic evaluations and aggressive management of the underlying lung disease (**Table V**; available at www.jpeds.com). PH-targeted therapy should be initiated only with echo- or cath-derived evidence of significant PH. Echo measurements that may be considered significant are a TRJV >3 m/second estimated RV/LVSP >0.5, and septal flattening in the absence of a significant left to right shunt. Cath measurements considered significant include a ratio of pulmonary artery to systemic pressure ≥0.5, indexed PVR ≥3 WU or Rp:Rs ≥0.5, and a normal wedge or left ventricle end diastolic pressure without evidence of significant PVS.[6]

In infants with evidence of sustained PH, after treatment of underlying conditions, pharmacologic therapy is often initiated. The widest experience reported in the literature favors the use of sildenafil, a PDE-5 inhibitor that modulates the NO-cyclic GMP signaling pathway.[64,67] Studies of sildenafil therapy in children with BPD-PH are limited, but supportive data include a demonstration of its efficacy in the treatment of PPHN,[66,68] and its safety and possible efficacy during long-term therapy in older children with BPD-PH. Sildenafil dosing in the NICU is initiated at 0.3-0.5 mg/kg/dose orally every 8 hours and can be gradually increased to a maximum of 3 mg/kg/day, divided every 6-8 hours. If the infant cannot be treated enterally, an intravenous dose of half the calculated oral dose is given over 1 hour with careful blood pressure monitoring. Sildenafil may increase the incidence of gastroesophageal reflux, and some providers opt to start H2 blockers concomitantly.[69] Some institutions use an endothelin receptor antagonist (bosentan) as initial therapy, starting at 0.5-1 mg/kg every 12 hours and increasing after 2-4 weeks to 2 mg/kg twice a day with liver enzyme monitoring every 4 weeks or earlier during respiratory or other infections.

Once a medication is initiated, close clinical monitoring with serial echo and NT-proBNP or BNP levels along with frequent clinical assessment define the response to therapy and need for combination treatment. Because there is limited literature on the safety profile of these medications, especially with combination therapy, PH-specific drug therapy should be guided by a PH specialist. As discussed, catheterization or other imaging modalities may be useful to better define interventions in poorly responsive patients, especially prior to starting a prostanoid.

Inhaled prostanoids, such as iloprost or epoprostenol, can be continuously or intermittently delivered every 2-4 hours (eg, with iloprost) through the ventilator or via nasal prongs.[7,70] The

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use of inhaled prostanoids may be associated with fewer systemic side effects than intravenous prostanoids.[71] Recent studies have shown that subcutaneous treprostinil is safe in infants, and site pain may be less of an issues in this subgroup compared with that previously reported in adults.[72] Concerns regarding the potential for parenteral prostanoids to worsen gas exchange in the setting of heterogeneous lung disease because of ventilation-perfusion mismatching have been raised. These concerns, however, in clinical practice seem more theoretical than true.[71]

Adverse effects of pulmonary vasodilator therapy can include systemic hypotension, gastroesophageal reflux with worsened feeding problems and aspiration risks, pulmonary edema exacerbated by postcapillary hypertension (pulmonary venous or LV diastolic dysfunction), and possible increased airway congestion. Short-term effects of calcium channel blockers (CCBs) in infants with BPD have been studied in infants with BPD during cardiac catheterization.[73,74] These studies showed that CCBs can cause acute pulmonary vasodilation; however, these studies were performed while most subjects were hypoxic, and the addition of supplemental oxygen alone had similar effects on pulmonary hemodynamics without tachycardia in this cohort.[73,74] A more recent study of acute vasoreactivity testing with iNO in infants with BPD showed that the acute response to CCB was poor, especially in comparison with iNO and brief hyperoxia, and that some infants developed systemic hypotension.[49] Concerns persist that young infants with PH, especially with evidence of impaired myocardial contractility, may worsen with CCB therapy, and caution is urged, especially with the initiation of CCB therapy.[6]

Monitoring Therapeutic Response and Late Outcomes

Recommendation #11: Infants with PH and BPD should have outpatient follow-up with the multidisciplinary PH team for ongoing treatment of their chronic lung disease and PH at intervals of 3-4 months with use of echocardiography, biomarkers, hemodynamic studies, and sleep studies when indicated during follow-up, depending on disease severity and clinical progress. (class I, LOE B)

Rationale: In addition to close monitoring of pulmonary status, infants with BPD-PH should be followed by serial echos, and BNP or NT-proBNP levels at 3- to 4-month intervals in the setting of stable disease.[19,20,44] Currently, there is limited evidence on the appropriate duration of PH therapies in this population.[14,17,18,66] If the PH gradually resolves over time with lung growth, medications can be gradually tapered or the infant simply allowed to "outgrow the dose" before complete discontinuation of PH-targeted drugs. Continued monitoring for new respiratory signs, exercise intolerance, or reduced activity and a repeat echocardiogram is recommended after stopping PH medications, usually within 1-2 months. Abrupt worsening of PH may reflect several factors, including the lack of compliance with oxygen therapy or medication use, but can be related to the progressive development of an intercurrent infection, respiratory exacerbations with worsening airways or lung disease (eg, obstructive sleep apnea, aspiration, reactive airways disease, unrecognized airway lesions, and others), pulmonary vein stenosis or other complications. Some infants with resolved PH have signs and echo findings of worsening during an acute viral infection. If PH persists after the inciting infection has resolved, PH-targeted drug therapy may be initiated or added and continued until serial echocardiograms show resolution of disease. Concurrent use of BNP or NT-proBNP may aid clinical decision making, but do not specifically diagnose PH nor should be used to direct therapy in isolation from clinical and echocardiogram findings.

We recommend weaning medications after serial echos document resolution of PH. Monitoring BNP or NT proBNP levels may be useful to augment therapeutic decision making during follow-up. The use of supplemental oxygen therapy to maintain consistent oxygen saturations in the 92%-95% range is recommended in these infants, and often low dose oxygen is continued in these infants as PH therapy is being weaned off. The use of periodic home pulse oximetry studies may enable more successful weaning from supplemental oxygen, but formal sleep polysomnography is recommended for patients with sustained oxygen requirements, especially with sleep.

Conclusions

Pulmonary vascular disease and PH contribute to the pathogenesis and pathophysiology of BPD and significantly influence the outcomes of preterm infants with BPD. Persistent echocardiographic evidence of PH beyond the first few months of life has been associated with high mortality, especially in infants with severe disease who require prolonged support with mechanical ventilation. Ongoing care of infants with BPD-PH requires comprehensive and consistent management based on current levels of evidence. The lack of strong data from randomized clinical trials and other sources makes this statement of consensus recommendations from a multidisciplinary group of experienced PH clinicians on the diagnosis, evaluation, management, and overall care of children with BPD and PH very timely and important. Consensus guidelines for the diagnosis, evaluation, and management of PH in infants with established BPD have been published; however, many aspects of care remain controversial, largely because of the lack of strong evidence-based data. This report presents the consensus patient care recommendations developed by PPHNet, a multidisciplinary group of neonatologists, cardiologists, pulmonologists, intensivists, and others. Overall, a consistent best evidence-based approach may improve early and late cardiopulmonary outcomes after preterm birth, but further studies of the natural history, late outcomes, and impact of therapeutic interventions for the prevention and treatment of PH in established BPD are needed. These recommendations provide practical guidelines and simple care algorithms that can be enhanced through future studies that include short- and long-term outcome assessments. ■

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Appendix

Additional member of the PPHNet Study Group include:

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Table I. Summary of recommendations

	Recommendations
1	A multidisciplinary team of neonatologists, pulmonologists, cardiologists, intensivists, and PH specialists, should be involved in the care of infants with BPD-PH to ensure a comprehensive and consistent approach. (I,C)
2	Screening echocardiograms should be performed in preterm infants in the following settings: (1) severe hypoxemic respiratory failure despite optimized ventilator therapy (I,B); (2) with sustained need for high FiO_2 and ventilator support throughout the clinical course (I,B); (3) continued need for ventilator support at postnatal d 7 (I,C); and (4) at the time of formal BPD diagnosis per current practice (36 wk PMA) (I,B)
3	Echocardiography should include full characterization of physiologic contributions of structural abnormalities, shunts and pulmonary veins, including specific evaluation of right and left ventricular size, hypertrophy, and function, interventricular septal position and attempts to accurately assess tricuspid and pulmonary regurgitation jet velocities. (I,B)
4	BNP/NT-ProBNP levels can aid clinical decision making, but these tests do not replace the use of echocardiogram or cardiac catheterization for PH assessment (I,B)
5	Evaluation and treatment of comorbidities that impact the severity of lung disease should be undertaken with the diagnosis of PH in BPD infants before the initiation of PAH-targeted therapy. (I,B)
6	Cardiac catheterization should be performed prior to escalation of therapies when safe and feasible to define the severity of PH and to evaluate shunt physiology and the presence of left ventricular dysfunction, pulmonary vein stenosis, and aortopulmonary collaterals. (I,B)
7	Supplemental oxygen therapy should be used to avoid episodic or sustained hypoxemia and with the goal of maintaining O_2 saturations between 92%-95% in patients with established BPD and PH (I,B).
8	iNO_2 is indicated to treat severe PH, especially with acute PH exacerbations and rapid disease progression (I,B)
9	PH-targeted therapy should be considered for infants with BPD and sustained PH after optimal treatment of underlying respiratory and cardiac disease (I,B)
10	PH specialists should guide decisions regarding selection, initiation and modification of targeted therapy based on clinical, biomarker, echocardiographic and hemodynamic evidence of disease severity; drug tolerance (and availability/cost). (I,B)
11	Multidisciplinary team outpatient follow up at 3-4 months intervals is necessary for monitoring progress and modifying therapy, with the use of serial echocardiography, and biomarkers, hemodynamic studies and respiratory evaluations, including sleep studies, when indicated. (I,B)

PAH, pulmonary arterial hypertension.

Table V. Cardiac catheterization protocol for BPD infants

Initial hemodynamics performed under baseline conditions1
- Hemodynamic measurements:
  - RA pressures (a,v,mean)
  - RV pressures (systolic, end diastolic)
  - Main, left and right PAPs (systolic, diastolic, mean)
- Systemic arterial pressures (systolic, diastolic, mean)
  - Left atrial (LA) or pulmonary capillary wedge pressure (PCWP) (a,v,mean)
  - Cardiac index (by thermodilution for patients without shunt lesions)
  - Oximetry (SVC, RA, RV, PA, pulmonary veins, LA, LV, aorta or femoral artery)
  - Systemic arterial blood gas
- Hemodynamic calculations
  - PVRi WU*m^2
  - SVRi WU*m^2
  - PVRi/SVRi
  - Qp and Qs (by Fick for patients with shunt lesions)
  - Qp:Qs

Conditions for hemodynamic data collection:
1. Baseline (FiO_2 to maintain normoxia-Sats 92%-95%)
2. 100% oxygen (systemic saturation target > 95%)
3. 100% oxygen + iNO (40 ppm)
4. Baseline*

Pulmonary angiograms to assess pulmonary artery stenosis (if indicated)
Pulmonary venograms to assess for stenosis/obstruction
Pulmonary wedge angiography to assess capillary bed morphometry/pathology
Aortogram to assess for aortopulmonary collateral vessels

1. Consideration should be given to whether procedure is performed under conscious sedation or general anesthesia based on patient safety. However, effort should be directed to using the minimum sedation possible to maintain hemodynamic and gas exchange targets that mimic the patient's baseline state. Correct blood gas to maintain near normal PH
2. Consideration should be given to the amount of diuretic the patient receives when interpreting these values. High normal pressures in the faces of high dose diuretics may be suggestive of LV dysfunction.
3. All hemodynamic measurements and calculations should be repeated for every condition.

PVRi, pulmonary vascular resistance index; *SVRi*, systemic vascular resistance index.

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