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