Pediatric Pulmonary Hypertension

Guidelines From the American Heart Association and American Thoracic Society

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Abstract—Pulmonary hypertension is associated with diverse cardiac, pulmonary, and systemic diseases in neonates, infants, and older children and contributes to significant morbidity and mortality. However, current approaches to caring for pediatric patients with pulmonary hypertension have been limited by the lack of consensus guidelines from experts in the field. In a joint effort from the American Heart Association and American Thoracic Society, a panel of experienced clinicians and clinician-scientists was assembled to review the current literature and to make recommendations on the diagnosis, evaluation, and treatment of pediatric pulmonary hypertension. This publication presents the results of extensive literature reviews, discussions, and formal scoring of recommendations for the care of children with pulmonary hypertension. (***Circulation*. 2015;132:2037-2099. DOI: 10.1161/CIR.0000000000000329.**)

Key Words: AHA Scientific Statements ■ bronchopulmonary dysplasia ■ congenital diaphragmatic hernia ■ congenital heart disease ■ genetics ■ persistent pulmonary hypertension of the newborn ■ sickle cell disease

†Deceased.

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1. Introduction

1.1. Rationale and Goals

This guidelines document addresses approaches to the evaluation and treatment of pulmonary hypertension (PH) in children, defined as a resting mean pulmonary artery pressure (mPAP) >25 mm Hg beyond the first few months of life. This document focuses on childhood disorders of PH resulting from pulmonary vascular disease (PVD) and includes PH related to cardiac, lung, and systemic diseases, as well as idiopathic pulmonary artery hypertension (IPAH). IPAH is a pulmonary vasculopathy that remains a diagnosis of exclusion, specifically indicating the absence of diseases of the left side of the heart or valves, lung parenchyma, thromboembolism, or other miscellaneous causes. The term PVD is also commonly used in the setting of pediatric diseases of the lung circulation. PVD is a broader and more inclusive term than PH in that it includes abnormalities of vascular tone, reactivity, growth, and structure that may exist without the development of increased PAP. For example, abnormal pulmonary vascular growth, structure, or function may impair pulmonary blood flow and cardiac performance in disorders associated with single ventricle physiology, yet mPAP may not be sufficiently elevated to qualify as PH (Table 1).

PH and related PVD cause significant morbidity and mortality in diverse childhood diseases. Despite the availability of new drug therapies, long-term outcomes for children with severe PAH remain poor. As in adult PAH, IPAH in pediatric patients can be devastating and often contributes to poor outcomes.[1] Unfortunately, whereas the adult PAH literature is a robust with several treatment guidelines, few studies specifically address the safety and efficacy of therapies in children, and there are no treatment guidelines. Indeed, most studies of potential PAH therapeutics have focused on adults and, because of the nature of adult PAH, have generally been conducted in patients with a limited range of associated conditions.[2] Thus, pediatric PH has been understudied, and little is understood about the natural history, fundamental mechanisms, and treatment of childhood PH.

Limitations for performing adequate studies of the pediatric population include the many associated conditions that fragment the classification of pediatric PH, the relatively small numbers of PAH patients at each center, the scarcity of multidisciplinary pediatric PAH programs, the lack of a national PH network, and suboptimal communication between scientists and clinicians.[3] There is clearly a need to better define the natural history and course of pediatric PAH, to develop new strategies to identify patients at risk for the development of PAH, and to establish novel approaches to diagnose, to monitor the disease progression of, and to treat children with PAH.[4]

Pediatric PH is distinct from adult PH in several ways. Most important, pediatric PH is intrinsically linked to issues of lung growth and development, including many prenatal and early postnatal influences.[3] The development of PH in the neonate and young infant is often related to impaired functional and structural adaptation of the pulmonary circulation during transition from fetal to postnatal life. The timing of pulmonary vascular injury is a critical determinant of the subsequent response of the developing lung to such adverse stimuli, including hyperoxia, hypoxia, hemodynamic stress, and inflammation. Beyond the hemodynamic effects of lung vascular development, normal maturation of the lung circulation plays critical roles in lung organogenesis and the development of the distal airspace. Thus, a normal pulmonary vascular bed is required for maintenance of lung structure, metabolism, and gas exchange and confers the ability to tolerate increased workloads imposed by exercise.

Preclinical studies suggest that angiogenesis in the lung influences alveogenesis and conversely that disruption of lung vascular growth can impair distal airspace structure and contributes to the pathobiology of diverse lung diseases. In addition, perinatal factors may contribute to an increased risk for the late development of PH in adulthood, leading to the speculation that an important window may exist for early identification of susceptibility factors or interventions. Finally, adult PH and pediatric PH differ in vascular function and structure, genetics, natural history, response of the right ventricle (RV), and responsiveness to PAH-specific therapies. It is important to note that many more conditions are associated with PH in children than in adults, casting some doubt about the direct applicability of the adult classification system and treatment guidelines to children. Therapeutic strategies for adult PAH have not been sufficiently studied in children to allow definition of potential toxicities or optimal dosing. Moreover, clinical research in pediatric PH suffers from a lack of age-appropriate clinical end points.

Gaps in our current knowledge of basic and clinical science behind pediatric PH were recently highlighted in a National Heart, Lung, and Blood Institute workshop.[4] This workshop highlighted a critical need to better characterize unique aspects of the developing lung circulation and basic mechanisms of disease. It also identified factors that limit the ability to perform clinical trials in children with PH or related PVD, including the lack of established biomarkers that can predict disease risk, severity, and disease progression. We currently lack sufficient outcome measures that are applicable to

Table 1. PH: Definitions

PH
mPAP ≥25 mm Hg in children >3 mo of age at sea level
PAH
mPAP ≥25 mm Hg
PAWP <15 mm Hg
PVRI >3 WU × M^2
IPAH or isolated PAH
PAH with no underlying disease known to be associated with PAH
Referred to as HPAH with positive family or genetic evaluation
PHVD
Broad category that includes forms of PAH but includes subjects with elevated TPG (mPAP−left atrial pressure or PAWP >6 mm Hg) or high PVRI as observed in patients with cavopulmonary anastomoses without high mPAP

HPAH indicates heritable pulmonary artery hypertension; IPAH, idiopathic pulmonary artery hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary artery hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PHVD pulmonary hypertensive vascular disease; PVRI, pulmonary vascular resistance index; and TPG, transpulmonary pressure gradient.

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young children with PH and need to develop and apply age- and disease-specific therapies for pediatric PH.

1.2. Scope of Project

To address this need, a working group of clinicians and clinician-scientists was established to create a guidelines document for the care of children with PAH under the auspices of the American Heart Association (AHA) and American Thoracic Society (ATS). Members of this committee were carefully vetted by the AHA and ATS to ensure broad experience in diverse forms of pediatric PAH from both clinical and research perspectives. The goal of this group was to define a comprehensive set of clinical care guidelines based on an extensive literature review and expert opinion. The results of this process are presented as a series of recommendations that are graded to reflect the quality of the evidence. While recognizing the lack of extensive clinical research in children and a significant paucity of multicenter, randomized trials, this group worked toward developing practical guidelines that reflect the current state of the art in the field. These guidelines are intended to assist healthcare providers in clinical decision making by describing generally acceptable approaches to the diagnosis and management of children with PAH. It is acknowledged that in many cases recommendations are based on the consensus of expert opinion (Level C) rather than the results of multiple randomized, controlled, clinical trials (RCTs; Level A). The guidelines attempt to define practices that meet the needs of most patients in most circumstances. Naturally, decisions about the care of a specific patient must be made by the practitioner in light of all of the circumstances presented by the patient and family. As a result, there will likely be clinical settings in which decisions that differ from these guidelines might be appropriate. Decisions should also involve consideration of the expertise at the specific center where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care.

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1.3. Methods

1.3.1. Committee Composition

An expert panel was selected and rigorously reviewed by members of the AHA and ATS to develop these guidelines, to grade the level of clinical evidence, and to write recommendations based on the current knowledge of diagnosis, evaluation, and treatment of pediatric PH. As a start, leading clinicians and clinician-scientists from the pediatric PH field were selected from medical centers with strong clinical care and research programs throughout North America. This original group was multidisciplinary by design and included pediatric pulmonologists, pediatric and adult cardiologists, pediatric intensivists, neonatologists, and translational scientists. Additional members of the committee were selected on the basis of recommendations made by the Pediatric Assembly of the ATS and the Practice Guidelines Committee of the AHA to participate in this project.

1.3.2. Disclosure of Conflicts of Interest

Every effort was made by members of the task force to avoid actual, potential, or perceived conflicts of interest. Conflicts of interest and relationships with industry were rigorously vetted by the ATS and AHA. All members of the committee completed conflict of interest declarations that were reviewed by the ATS and AHA. The AHA conflict of interest policy specifically directs that members of the committee avoid any direct or indirect conflict between their personal, professional, and business interests and the interests of the AHA. The AHA Inclusiveness Policy, Core Values, and Ethics Policy provided additional guidelines for the working group. Each individual considered for participation for this guidelines committee reported all relationships with industry, and the final composition of this committee was based on extensive review of these reports by the AHA before any formal committee activities to ensure that project leaders and >50% of the committee had no significant conflicts of interest at assignment.

1.3.3. Committee Meetings and Evidence Review Process

Subgroups from within the overall team were formed to focus on specific areas for each of the key topics. The overall planning of the document was based on meetings, teleconferences, and email distribution of materials related to this document. Overall, plans for document structure, content, and scoring were made through 4 face-to-face group meetings, including sessions held in conjunction with the ATS International Conference in New Orleans (2010), Denver (2011), and San Francisco (2012). An additional meeting was held during the Pediatric Pulmonary Hypertension Meeting in San Francisco (2011), and another grading session was held by teleconference to finalize remaining recommendations after our final face-to-face grading session (2012). Each subgroup presented specific questions for review and analysis, which were approved by task force members. After submission for AHA/ATS peer review in 2013, a revision was reviewed by the committee at the ATS meeting in San Diego (2014) before resubmission.

1.3.4. Literature Review and Preparation of Evidence Profiles

1.3.4.1. Search Strategy

The initial approach was to organize a comprehensive literature review on disorders associated with PH in children, as well as diagnostic, evaluation, and therapies for PH in diverse settings. This approach included an extensive search performed by medical librarians with experience in performing literature searches for previous guidelines task forces (Rosalind Dudden and her staff at the National Jewish Center, Denver, CO). Comprehensive literature reviews were performed with PubMed and Ovid Medline and made available through a common task force Web site. Standard search terms such as pulmonary hypertension and pediatric pulmonary hypertension were used. Other search terms addressed diseases associated with PH (eg, bronchopulmonary dysplasia [BPD], sickle cell disease [SCD], and congenital heart disease [CHD]), PAH-specific drugs, and other related subjects (Supplemental Figure). Additional searches to supplement the primary data review were performed periodically, at least annually, over the time of the project by individual task forces and by the writing group.

1.3.5. Quality of Evidence and Strength of Recommendations

The task force used evidence-based AHA methodologies to analyze the data and to develop recommendations (as based on the American College of Cardiology Foundation/AHA Clinical Practice Guideline Methodology Summit Report[4a]). The approach for scoring the evidence and its strength is presented in Table 2, which includes phrases that express the strength of each recommendation. The Class of Recommendation is an estimate of the magnitude of the treatment effect, with consideration given to risks versus benefits and the evidence and agreement that a given treatment or procedure is or is not useful or effective (Class I or II). Class III designation is applied for interventions that may cause harm to the patient. The Level of Evidence is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation, with the weight of evidence ranked as Level of Evidence A, B, or C according to specific definitions (Table 2). For conditions in which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as Level of Evidence C. The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple RCTs or meta-analyses. The committee ranked

Table 2. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit — is not recommended; is not indicated; should not be performed/administered/other; is not useful/beneficial/effective COR III: Harm — potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/administered/other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

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available evidence as Level B when data were derived from a single RCT or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. The panel met to provide final discussions and scoring of the quality of evidence that supports the guidelines. The guideline recommendations and scoring (Class of Recommendation and Level of Evidence) were approved by an open vote. The specific language used to express each recommendation was based on the AHA's standardized format for articulating recommendations based on Class of Recommendation and Level of Evidence (Supplemental Table). Each recommendation was stated as clearly as possible with the intent to be as specific as possible for defining referent populations, actions, and related issues. The decision to use the AHA Class of Recommendation/Level of Evidence guidelines methodology was based on discussions and agreements with the ATS before the project was launched. The Supplemental Table summarizes differences in language used by different methodologies (from the American College of Cardiology Foundation/AHA Clinical Practice Methodology Summit Report[4a]).

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Summary of Recommendations

Diagnostics, Assessments, and Monitoring

1. **At the time of initial PH diagnosis, a comprehensive history and physical examination, combined with diagnostic testing for assessment of PH pathogenesis/classification and formal assessment of cardiac function, should be performed before the initiation of therapy at an experienced center *(Class I; Level of Evidence B)*.**
2. **Imaging to diagnose pulmonary thromboembolic disease, peripheral pulmonary artery stenosis, pulmonary vein stenosis, pulmonary veno-occlusive disease (PVOD), and parenchymal lung disease should be performed at the time of diagnosis *(Class I; Level of Evidence B)*.**
3. **After a comprehensive initial evaluation, serial echocardiograms should be performed. More frequent echocardiograms are recommended in the setting of changes in therapy or clinical condition *(Class I; Level of Evidence B)*.**
4. **Cardiac catheterization is recommended before initiation of PAH-targeted therapy (*Class I; Level of Evidence B*). Exceptions may include critically ill patients requiring immediate initiation of empirical therapy (*Class I; Level of Evidence B*).**
5. **Cardiac catheterization should include acute vasoreactivity testing (AVT) unless there is a specific contraindication (*Class I; Level of Evidence A*).**
6. **The minimal hemodynamic change that defines a positive response to AVT for children should be considered as a ≥20% decrease in PAP and pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) without a decrease in cardiac output (*Class I; Level of Evidence B*).**
7. **Repeat cardiac catheterization is recommended within 3 to 12 months after initiation of therapy to evaluate response or with clinical worsening (*Class I; Level of Evidence B*).**
8. **Serial cardiac catheterizations with AVT are recommended as follows:**
   a. **Serial cardiac catheterizations should be done during follow-up to assess prognosis and potential changes in therapy (*Class I; Level of Evidence B*)**
   b. **Intervals for repeat catheterizations should be based on clinical judgment but include worsening clinical course or failure to improve during treatment (*Class I; Level of Evidence B*).**
9. **Magnetic resonance imaging (MRI) can be useful as part of the diagnostic evaluation and during follow-up to assess changes in ventricular function and chamber dimensions (*Class IIa; Level of Evidence B*).**
10. **Brain natriuretic peptide (BNP) or N-terminal (NT) proBNP should be measured at diagnosis and during follow-up to supplement clinical decision (*Class I; Level of Evidence B*).**
11. **The 6-minute walk distance (6MWD) test should be used to follow exercise tolerance in pediatric PH patients of appropriate age (*Class I; Level of Evidence A*).**
12. **The recommendations for a sleep study are the following:**
    a. **A sleep study should be part of the diagnostic evaluation of patients with PH at risk for sleep-disordered breathing (*Class I; Level of Evidence B*).**
    b. **A sleep study is indicated in the evaluation of patients with poor responsiveness to PAH-targeted therapies (*Class I; Level of Evidence B*).**

Genetics

1. **Genetic testing with counseling can be useful for children with IPAH or in families with heritable PAH (HPAH) to define the pathogenesis, to identify family members at risk, and to inform family planning (*Class IIa; Level of Evidence C*).**
2. **Recommendations for genetic testing of first-degree relatives of patients with monogenic forms of HPAH include the following:**
   a. **Genetic testing is indicated for risk stratification (*Class I; Level of Evidence B*).**
   b. **Genetic testing is reasonable to screen asymptomatic carriers with serial echocardiograms or other noninvasive studies. (*Class IIa; Level of Evidence B*).**
3. **Members of families afflicted with HPAH who develop new cardiorespiratory symptoms should be evaluated immediately for PAH (*Class I; Level of Evidence B*).**
4. **Families of patients with genetic syndromes associated with PH should be educated about the symptoms of PH and should be counseled to seek evaluation of the affected child should symptoms arise (*Class I; Level of Evidence B*).**

Persistent PH of the Newborn

1. **Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation**

(ECMO) support in term and near-term infants with persistent PH of the newborn (PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (*Class I; Level of Evidence A*).
2. Lung recruitment strategies can improve the efficacy of iNO therapy and should be performed in patients with PPHN associated with parenchymal lung disease (*Class I; Level of Evidence B*).
3. ECMO support is indicated for term and near-term neonates with severe PH or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function (*Class I; Level of Evidence A*).
4. Evaluation for disorders of lung development such as alveolar capillary dysplasia (ACD) and genetic surfactant protein diseases is reasonable for infants with severe PPHN who fail to improve after vasodilator, lung recruitment, or ECMO therapy (*Class IIa; Level of Evidence B*).
5. Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to iNO, especially with an oxygenation index that exceeds 25 (*Class IIa; Level of Evidence B*)
6. Inhaled prostacyclin (PGI_2) analogs may be considered as adjunctive therapy for infants with PPHN who are refractory to iNO and have an oxygenation index that exceeds 25 (*Class IIb; Level of Evidence B*).
7. Intravenous milrinone is reasonable in infants with PPHN and signs of left ventricular (LV) dysfunction (*Class IIb; Level of Evidence B*).
8. iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (*Class IIa; Level of Evidence B*).

Congenital Diaphragmatic Hernia

1. Minimizing peak inspiratory pressure and avoiding large tidal volumes is recommended to reduce ventilator-associated acute lung injury in infants with congenital diaphragmatic hernia (CDH) (*Class I; Level of Evidence B*).
2. High-frequency oscillatory ventilation is a reasonable alternative mode of ventilation for subjects with CDH when poor lung compliance, low volumes, and poor gas exchange complicate the clinical course (*Class IIa; Level of Evidence A*).
3. iNO therapy can be used to improve oxygenation in infants with CDH and severe PH but should be used cautiously in subjects with suspected LV dysfunction (*Class IIa; Level of Evidence B*).
4. ECMO is recommended for patients with CDH with severe PH who do not respond to medical therapy (*Class I; Level of Evidence B*).
5. Prostaglandin E_1 may be considered to maintain patency of the ductus arteriosus and to improve cardiac output in infants with CDH and suprasystemic levels of PH or RV failure to improve cardiac output (*Class IIb; Level of Evidence C*).
6. Evaluation for long-term PAH-specific therapy for PH in infants with CDH should follow recommendations for all children with PH, which include cardiac catheterization (*Class I; Level of Evidence B*).
7. Longitudinal care in an interdisciplinary pediatric PH program is recommended for infants with CDH who have PH or are at risk of developing late PH (*Class I; Level of Evidence B*).

Bronchopulmonary Dysplasia

1. Screening for PH by echocardiogram is recommended in infants with established BPD (*Class I; Level of Evidence B*).
2. Evaluation and treatment of lung disease, including assessments for hypoxemia, aspiration, structural airway disease, and the need for changes in respiratory support, are recommended in infants with BPD and PH before initiation of PAH-targeted therapy (*Class I; Level of Evidence B*).
3. Evaluation for long-term therapy for PH in infants with BPD should follow recommendations for all children with PH and include cardiac catheterization to diagnose disease severity and potential contributing factors such as LV diastolic dysfunction, anatomic shunts, pulmonary vein stenosis, and systemic collaterals (*Class I; Level of Evidence B*).
4. Supplemental oxygen therapy is reasonable to avoid episodic or sustained hypoxemia and with the goal of maintaining O_2 saturations between 92% and 95% in patients with established BPD and PH. (*Class IIa; Level of Evidence C*).
5. PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying respiratory and cardiac disease (*Class IIa; Level of Evidence C*).
6. Treatment with iNO can be effective for infants with established BPD and symptomatic PH (*Class IIa; Level of Evidence C*).
7. Serial echocardiograms are recommended to monitor the response to PAH-targeted therapy in infants with BPD and PH (*Class I; Level of Evidence B*).

Pharmacotherapy (Table 3)

1. Supportive care with digitalis and diuretic therapy is reasonable with signs of right heart failure but should be initiated cautiously (*Class IIb; Level of Evidence C*).
2. Recommendations for long-term anticoagulation with warfarin include the following:
   a. Warfarin may be considered in patients with IPAH/HPAH, patients with low cardiac output, those with a long-term indwelling catheter, and those with hypercoagulable states (*Class IIb; Level of Evidence C*);
   b. Targeting the therapeutic range for an international normalized ratio between 1.5 and 2.0 is recommended for young children with PAH (*Class I; Level of Evidence C*).
   c. Anticoagulation should not be used in young children with PAH because of concerns about

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Table 3. Pharmacological Therapy for Pediatric PH

Drug Class	Agent	Dosing	Adverse Effects	COR/LOE Comments
Digitalis	Digoxin	Usual age and weight dosing schedule 5 μg/kg orally twice daily up to 10 years, then 5 μg/kg once daily Maximum dose, 0.125 mg/d orally	Bradycardia is dose limiting and may limit effectiveness in PH	COR IIb LOE C Limited data and now rarely used in pediatric PH Not effective for acute deterioration Monitor renal function
Diuretics	Several agents	Loop diuretics, thiazides, and spirolactone are all dosed by weight and are not different than for other forms of heart failure	Care is needed because overdiuresis can reduce the preload of the failing RV	COR IIa LOE C
Oxygen	Oxygen	Flow rate as needed by nasal cannula to achieve target O_2 saturations	Too high a flow rate can dry the nares and cause epistaxis or rhinitis	COR IIb LOE C Oxygen is not usually prescribed for children with PH unless the daytime saturations are low (<92%) Polysomnography is helpful in delineating the need for O_2 therapy at night May be helpful for symptomatic class IV patients
Vitamin K antagonists (anticoagulation)	Warfarin	Goal INRs in the range of 1.5–2.0 are usually chosen for this indication Higher INR may be needed for history of thrombosis or hypercoagulability	Risk of anticoagulation in pediatrics must be balanced with the hypothetical benefits Teratogenic effects	For IPAH/HPAH: COR IIa LOE C Use of warfarin in children before they are walking well or with developmental or neurological problems, including seizures or syncope, adds risk May be useful in PH with heart failure, central venous line, or right-to-left shunt Use of warfarin in patients with hypercoagulable state is reasonable For APAH: COR IIb LOE C Use of warfarin in this population is poorly studied Use of warfarin in patients with hypercoagulable state is reasonable
CCB	Nifedipine	Starting dose: 0.1–0.2 mg/kg orally 3 times daily Dose range: 2–3 $mg \cdot kg^{-1} \cdot d^{-1}$ Maximum adult dose: 180 mg/d orally Always uptitrate from a lower dose If possible, use extended-release preparations	Bradycardia Decreased cardiac output Peripheral edema Rash Gum hyperplasia Constipation	COR I LOE B Duration of benefit may be limited even with initial favorable response; periodic repeat assessments for responsiveness are indicated
CCB	Diltiazem	Starting dose: 0.5 mg/kg orally 3 times daily Dose range: 3–5 $mg \cdot kg^{-1} \cdot d^{-1}$ orally Maximum adult dose: 360 mg/d orally Always uptitrate from a lower dose If possible, use extended-release preparations	Bradycardia Decreased cardiac output Peripheral edema Rash Gum hyperplasia Constipation	COR I LOE B Duration of benefit may be limited even with initial favorable response; periodic repeat assessments for responsiveness are indicated May cause bradycardia more than other CCBs Suspension useful in younger children
CCB	Amlodipine	Starting dose: 0.1–0.3 $mg \cdot kg^{-1} \cdot d^{-1}$ orally Dose range: 2.5–7.5 mg/d orally Maximum adult dose: 10 mg/d orally Always uptitrate from a lower dose	Bradycardia Decreased cardiac output Peripheral edema Rash Gum hyperplasia Constipation	COR I LOE B Duration of benefit may be limited even with initial favorable response

(*Continued*)

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Table 3. Continued

Drug Class	Agent	Dosing	Adverse Effects	COR/LOE Comments
PDE5 inhibitor	Sildenafil	Age <1 y: 0.5–1 mg/kg 3 times daily orally Weight <20 kg: 10 mg 3 times daily orally Weight >20 kg: 20 mg 3 times daily orally Delay use in extremely preterm infants until retinal vascularization is established	Headache Nasal congestion Flushing Agitation Hypotension Vision and hearing loss may be concerns Priapism Avoid nitrates	COR I LOE B Avoid higher dosing in children because a greater risk of mortality was noted in the STARTS-2 study in children with IPAH treated with high-dose sildenafil monotherapy Sildenafil approved in Europe and Canada FDA warning for use in children 1–17 y of age
PDE5 inhibitor	Tadalafil	Starting dose: 0.5–1 $mg \cdot kg^{-1} \cdot d^{-1}$ Maximum dose: 40 mg orally daily Evaluated only in children >3 y of age	Headache Nasal congestion Flushing Agitation Hypotension Vision and hearing loss may be concerns Priapism Nosebleeds Avoid nitrates	COR IIa LOE B Once-daily dosing Safety and efficacy data in children are limited
ERA	Bosentan (dual ET_A and ET_B antagonist)	Starting dose is half the maintenance dose Maintenance dose: Weight <10 kg: 2 mg/kg twice daily orally Weight 10–20 kg: 31.25 mg twice daily Weight >20–40 kg: 62.5 mg twice daily Weight >40 kg: 125 mg twice daily	Monthly LFTs required due to risk for hepatotoxicity HCG and pregnancy test required monthly Incidence of AST/ALT elevation is less in children compared with adults Fluid retention Teratogenicity Male infertility May decrease sildenafil level	COR I LOE B Data have been published on efficacy in Eisenmenger PH 2 Forms of birth control required Drug interaction with sildenafil
ERA	Ambrisentan (a highly selective ET_A antagonist)	Dose range: 5–10 mg orally daily Use in pediatric patients <5 y of age is unstudied	Routine LFTs recommended HCT and pregnancy test required Incidence of AST/ALT elevation is less in children compared with adults Fluid retention Teratogenicity Male infertility	COR IIa LOE B Safety and efficacy data in children are limited Avoid use in neonates or infant because glucuronidation is not mature
Prostacyclin	Epoprostenol (Flolan), Veletri (thermostable)	Continuous intravenous infusion Drug interaction with sildenafil Starting dose: 1–2 $ng \cdot kg^{-1} \cdot min^{-1}$ IV without a known maximum In pediatric patients, a stable dose is usually between 50 and 80 $ng \cdot kg^{-1} \cdot min^{-1}$ IV Doses >150 $ng \cdot kg^{-1} \cdot min^{-1}$ IV have been used Dose increases are required High-output syndrome at high doses can occur	Flushing, jaw, foot and bone pain, headaches, and diarrhea Systemic hypotension is possible Half-life is short (2–5 min), so PH crises occur rapidly if the infusion is stopped Icepack cooling and remixing every 24 h needed Central line complications occur	COR I LOE B Standard therapy for severe PH A temperature-stable formulation is available
Prostacyclin	Treprostinil (Remodulin)	Intravenous or subcutaneous: 2 Starting dose: 2 $ng \cdot kg^{-1} \cdot min^{-1}$ without a known maximum In pediatric patients, a stable dose is usually between 50 and 80 $ng \cdot kg^{-1} \cdot min^{-1}$ IV or SC Dose increases are required	Flushing, muscle pain, headaches, and diarrhea are common side effects Frequency and severity of side effects are less than with epoprostenol Elimination half-life is 4.5 h The drug is stable at room temperature Central line complications can occur, including Gram-negative infections with intravenous route Subcutaneous injection site pain may limit this route	For intravenous and subcutaneous: COR I LOE B
		Inhaled: 1–9 patient-activated breaths every 6 h Oral: dosing not fully evaluated in children	Inhaled drug can worsen reactive airway symptoms GI side effects may be greater than with intravenous, subcutaneous, or inhaled	For inhalation: COR IIa LOE B The nebulizer requires patient activation and controlled inhalation limited by age and development

(*Continued*)

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Table 3. Continued

Drug Class	Agent	Dosing	Adverse Effects	COR/LOE Comments
Prostacyclin	Iloprost (intermittent inhalation)	Pediatric dosing has not been determined but 6–9 inhalations per day are required, each lasting 10–15 min Start with 2.5-μg dose and uptitrate to 5-μg dose as tolerated	Flushing and headaches are common side effects Systemic hypotension is rare. Half-life is short Inhaled drug can worsen reactive airway symptoms	COR IIa LOE B In pediatrics, the dosing frequency may limit usefulness

ALT indicates alanine aminotransferase; APAH, pulmonary arterial hypertension associated with disease; AST, aspartate aminotransferase; CCB, calcium channel blocker; COR, class of recommendation; ERA, endothelin receptor antagonist; ET, endothelin; FDA, US Food and Drug Administration; GI, gastrointestinal; HCG, human chorionic gonadotropin; HCT, hematocrit; HPAH, heritable pulmonary arterial hypertension; INR, international normalized ratio; IPAH, idiopathic pulmonary arterial hypertension; LFT, liver function test; LOE, level of evidence; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension; RV, right ventricular; and STARTS, Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension.

COR and LOE grading are based on pediatric data.

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harm from hemorrhagic complications (*Class III; Level of Evidence C*).

3. **Oxygen therapy is reasonable for hypoxemic PAH patients who have oxygen saturations <92%, especially with associated respiratory disease (*Class IIa; Level of Evidence B*).**
4. **Recommendations for calcium channel blockers (CCBs) include the following:**
   a. **CCBs should be given only to those patients who are reactive as assessed by AVT and >1 year of age (*Class I; Level of Evidence C*).**
   b. **CCBs are contraindicated in children who have not undergone or are nonresponsive to AVT and in patients with right-sided heart dysfunction owing to the potential for negative inotropic effects of CCB therapy (*Class III; Level of Evidence C*).**
5. **Oral PAH-targeted therapy in children with lower-risk PAH is recommended and should include either a phosphodiesterase type 5 (PDE5) inhibitor or an endothelin (ET) receptor antagonist (ERA) (*Class I; Level of Evidence B*).**
6. **A goal-targeted therapy approach in which PAH-specific drugs are added progressively to achieve specified therapeutic targets can be useful (*Class IIa; Level of Evidence C*).**
7. **Intravenous and subcutaneous PGI_2 or its analogs should be initiated without delay for patients with higher-risk PAH (*Class I; Level of Evidence B*).**
8. **Recommendations for the transition from parenteral to oral or inhaled therapy include the following:**
   a. **This transition may be considered in asymptomatic children with PAH who have demonstrated sustained, near-normal pulmonary hemodynamics (*Class IIb; Level of Evidence C*).**
   b. **The transition requires close monitoring in an experienced pediatric PH center (*Class I; Level of Evidence B*).**

Idiopathic PAH

1. **Lung biopsy may be considered for children with PAH suspected of having PVOD, pulmonary capillary hemangiomatosis, or vasculitis (*Class IIb; Level of Evidence C*).**
2. **Referral to lung transplantation centers for evaluation is recommended for patients who are in World Health Organization (WHO) functional class III or IV on optimized medical therapy or who have rapidly progressive disease (*Class I; Level of Evidence A*).**
3. **Referral to a lung transplantation center for evaluation is recommended for patients who have confirmed pulmonary capillary hemangiomatosis or PVOD (*Class I; Level of Evidence B*).**

Pediatric Heart Disease

1. **In children with significant structural heart disease (ie, atrial septal defect [ASD], ventricular septal defect [VSD], and patent ductus arteriosus [PDA]) who have not undergone early repair (as generally defined as by 1 to 2 years of age, depending on the lesion and overall clinical status), the following are recommended:**
   a. **Cardiac catheterization should be considered to measure PVR index (PVRI) and to determine operability (*Class II; Level of Evidence B*).**
   b. **Repair should be considered if PVRI is <6 Wood units (WU)·m² or PVR/SVR <0.3 at baseline (*Class I; Level of Evidence B*).**
2. **In children with evidence of right-to-left shunting and cardiac catheterization revealing a PVRI ≥6 WU·m² or PVR/SVR ≥0.3, repair can be beneficial if AVT reveals reversibility of PAH (absolute PVRI <6 WU·m² and PVR/SVR <0.3) (*Class IIa; Level of Evidence C*).**
3. **If cardiac catheterization reveals a PVRI ≥6 WU·m² or PVR/SVR ≥0.3 and minimal responsiveness to AVT, the following are recommended:**
   a. **Repair is not indicated (*Class III; Level of Evidence A*).**
   b. **It is reasonable to implement PAH-targeted therapy followed by repeat catheterization with AVT after 4 to 6 months and to consider repair if the PVRI is <6 WU (*Class IIb; Level of Evidence C*).**

PH Crises/Acute RV Failure

1. **General postoperative strategies for avoiding PH crises (PHCs), including avoidance of hypoxia,**

acidosis, and agitation, should be used in children at high risk for PHCs (*Class I; Level of Evidence B*).
2. Induction of alkalosis can be useful for the treatment of PHCs (*Class IIa; Level of Evidence C*).
3. Administration of opiates, sedatives, and muscle relaxers is recommended for reducing postoperative stress response and the risk for or severity of PHCs (*Class I; Level of Evidence B*).
4. In addition to conventional postoperative care, iNO and/or inhaled PGI_2 should be used as the initial therapy for PHCs and failure of the right side of the heart (*Class I; Level of Evidence B*).
5. Sildenafil should be prescribed to prevent rebound PH in patients who have evidence of a sustained increase in PAP on withdrawal of iNO and require reinstitution of iNO despite gradual weaning of iNO dose (*Class I; Level of Evidence B*).
6. In patients with PHCs, inotropic/pressor therapy should be used to avoid RV ischemia caused by systemic hypotension (*Class I; Level of Evidence B*). Mechanical cardiopulmonary support should be provided in refractory cases (*Class I; Level of Evidence B*).
7. Atrial septostomy (AS) is recommended for patients with RV failure, recurrent syncope, or PHCs that persist despite optimized medical management but must be performed in an experienced PH center (*Class I; Level of Evidence B*).

Lung Diseases

1. Children with chronic diffuse lung disease should be evaluated for concomitant cardiovascular disease or PH by echocardiogram, especially those with advanced disease (*Class I; Level of Evidence B*).
2. Echocardiography is recommended to assess PH and RV function in patients with severe obstructive sleep apnea (OSA) (*Class I; Level of Evidence B*).
3. For exercise-limited patients with advanced lung disease and evidence of PAH, the following are recommended:
   a. A trial of PAH-targeted therapy is reasonable (*Class IIa; Level of Evidence C*).
   b. Catheterization of the right side of the heart may be considered (*Class IIb; Level of Evidence B*).

Hypobaric Hypoxia

1. Patients with symptomatic high altitude–related PH may be encouraged to move to low altitude (*Class IIb; Level of Evidence C*).
2. CCB therapy (with amlodipine or nifedipine) may be reasonable for high-altitude pulmonary edema (HAPE) prophylaxis in children with a previous history of HAPE (*Class IIb; Level of Evidence C*).
3. Therapy for symptomatic HAPE should include supplemental oxygen therapy and consideration of immediate descent (*Class I; Level of Evidence B*).
4. Children with HAPE should undergo evaluation to rule out abnormalities of pulmonary arteries or pulmonary veins, lung disease, or abnormal control of breathing (*Class I; Level of Evidence B*).

Systemic Disease

1. Early evaluation for PH, including a Doppler echocardiogram, is reasonable for children with hemolytic hemoglobinopathies or hepatic, renal, or metabolic diseases who develop cardiorespiratory symptoms (*Class IIa; Level of Evidence C*).
2. In children with chronic hepatic disease, an echocardiogram should be performed to rule out portopulmonary hypertension (PPHTN) and pulmonary arteriovenous shunt before they are listed for liver transplantation (*Class I; Level of Evidence B*).
3. It is reasonable for children with SCD to undergo an echocardiogram to screen for PH and associated cardiac problems by 8 years of age or earlier in patients with frequent cardiorespiratory symptoms (*Class IIa; Level of Evidence C*).
4. For children with SCD who have evidence of PH by echocardiogram, the following are recommended:
   a. Children with SCD should undergo further cardiopulmonary evaluation, including pulmonary function testing, polysomnography, assessment of oxygenation, and evaluation for thromboembolic disease (*Class I; Level of Evidence C*).
   b. Children with SCD should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (*Class I; Level of Evidence C*).
5. BNP and NT-proBNP measurements can be useful in screening for PH in patients with SCD (*Class IIa; Level of Evidence C*).
6. With the diagnosis of PH in children with SCD, optimization of SCD-related therapies (eg, blood transfusions, hydroxyurea, iron chelation, and supplemental oxygen) is recommended (*Class I; Level of Evidence C*).
7. PAH-targeted therapy should not be used empirically in SCD-associated PH because of potential adverse effects (*Class III; Level of Evidence C*).
8. PAH-targeted therapy may be considered in patients with SCD in whom there is confirmation of PH with marked elevation of PVR without an elevated pulmonary capillary wedge pressure by cardiac catheterization (*Class IIb; Level of Evidence C*).
9. A trial of a PGI_2 agonist or an ERA is preferred over PDE5 inhibitors in patients with markedly elevated PVR and SCD (*Class IIa; Level of Evidence B*).

Outpatient Care of Children With PH

1. Children with PH should be evaluated and treated in comprehensive, multidisciplinary clinics at specialized pediatric centers (*Class I; Level of Evidence C*).
2. Outpatient follow-up visits at 3- to 6-month intervals are reasonable, with more frequent visits for patients with advanced disease or after initiation of or changes in therapy (*Class IIa; Level of Evidence B*).
3. The following preventive care measures for health maintenance are recommended for pediatric patients with PH:

   • Respiratory syncytial virus prophylaxis (if eligible)
   • Influenza and pneumococcal vaccinations

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- **Rigorous monitoring of growth parameters**
- **Prompt recognition and treatment of infectious respiratory illnesses**
- **Antibiotic prophylaxis for the prevention of subacute bacterial endocarditis in cyanotic patients and those with indwelling central lines (*Class I; Level of Evidence C*).**

4. **Careful preoperative planning, consultation with cardiac anesthesia, and plans for appropriate postprocedural monitoring are recommended for pediatric patients with PH undergoing surgery or other interventions (*Class I; Level of Evidence C*).**
5. **Elective surgery for patients with pediatric PH should be performed at hospitals with expertise in PH and in consultation with the pediatric PH service and anesthesiologists with experience in the perioperative management of children with PH (*Class I; Level of Evidence C*).**
6. **As a result of significant maternal and fetal mortality associated with pregnancy in patients with PH, it is recommended that female adolescents with PH be provided with age-appropriate counseling about pregnancy risks and options for contraception (*Class I; Level of Evidence C*).**
7. **Because of the risks of syncope or sudden death with exertion, it is recommended that a thorough evaluation, including cardiopulmonary exercise testing (CPET) and treatment, be performed before the patient engages in athletic (symptom-limited) activities (*Class I; Level of Evidence C*).**
8. **Pediatric patients with severe PH (WHO functional class III or IV) or recent history of syncope should not participate in competitive sports (*Class III; Level of Evidence C*).**
9. **During exercise, it is recommended that pediatric patients with PH engage in light to moderate aerobic activity, avoid strenuous and isometric exertion, remain well hydrated, and be allowed to self-limit as required (*Class I; Level of Evidence C*).**
10. **During airplane travel, supplemental oxygen use is reasonable in pediatric patients with PH (*Class IIa; Level of Evidence B*).**
11. **Given the impact of childhood PAH on the entire family, children, siblings, and caregivers should be assessed for psychosocial stress and be readily provided support and referral as needed (*Class I; Level of Evidence C*).**

2. Definition, Classification, and Epidemiology of Pediatric Hypertension

Although the definition of PH in pediatrics is nearly identical to that applied to adults, some important differences exist (Table 1). PAP is similar to systemic arterial pressure in utero but rapidly falls after birth, generally achieving adult values by 2 to 3 months of postnatal age. After 3 months of age in term infants at sea level, PH is present when mPAP exceeds 25 mm Hg. However, the lack of elevated PAP does not exclude the presence of pulmonary hypertensive vascular disease (PHVD) in some settings. In particular, PVRI is important in the diagnosis and management of PHVD in children with CHD. For example, PHVD may exist with an mPAP <25 mm Hg in patients with CHD without a dedicated subpulmonary ventricle, especially if they have undergone cavopulmonary surgery. Conversely, in children with CHD and aortopulmonary or intracardiac shunts with increased pulmonary blood flow, PHVD may not be present even if the mPAP is ≥25 mm Hg. PVRI is generally not used to define PH, yet differentiating the relative influences of high or low pulmonary blood flow from vascular disease per se on PH, especially in the setting of CHD, remains a vital problem and a critical challenge for clinical decision making (see below).

Pediatric PH is currently categorized in fashion similar to adult PH, which is based on the WHO classification that was most recently revised at the Fifth World Symposium for Pulmonary Hypertension held in Nice, France (Table 4).[5] As a result of concerns about the applicability of an adult-focused system for the phenotypic heterogeneity of neonatal and childhood PH, the pediatric task force of the Pulmonary Vascular Research Institute, an international collaborative group created to promote global research in PH, proposed a novel system that may prove useful as a pediatric-specific system[6,7] (Table 5). The goal of the Panama Classification System is to highlight the phenotypic heterogeneity of PHVD from the fetus to the adolescent and the impact on diagnosis, treatment, and research.[7]

The Panama Classification System seeks to include heterogeneous and unique disorders that specifically present during early childhood, the importance of chromosomal and genetic syndromes, the impact of developmental mechanisms and physiology, and multiple factors that are often associated with pediatric PH. This classification system underscores the concept that signs of symptomatic PVD at all ages represent the balance between vascular growth through angiogenic mechanisms and vascular loss owing to genetic, epigenetic, or environmental pressures.[7] Although promising, this classification system needs to be tested, validated for utility, and refined for accuracy. This system also addresses the importance of the complexity of diverse clinical contributors to pediatric PH in a given patient. For example, scimitar syndrome may be associated with venous obstruction, the sequelae of high flow from aortopulmonary collaterals or anomalous pulmonary venous connection, and lung hypoplasia, making simple classification into one group or another difficult.

Overall, a diagnostic classification of neonatal and pediatric PHVD that reflects the clinical spectrum, genotype, and phenotype encountered in practice should be used for neonates and children with PHVD. However, more information is needed to determine whether a distinct pediatric classification system should be used in preference to the more traditional WHO system. Pediatric-specific registries and databases that accurately reflect the phenotype and genotype of neonatal and childhood PHVD may prove more helpful to better understand the natural history, critical factors that modulate outcomes and responses to therapies, and related research questions. In addition, a functional classification system with developmentally appropriate and objective indicators of symptoms should be used for neonates and children with PHVD.[6–11]

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Table 4. WHO Classification of Pulmonary Hypertension (Nice)

1. PAH
1.1 Idiopathic
1.2 Heritable
1.2.1 *BMPR2*
1.2.2 *ALK1, ENG, SMAD9, CAV1, KCNK3*
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 APAH
1.4.1 CTD
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 CHD
1.4.5 Schistosomiasis
1'. PVOD and/or PCH
1.1'' PPHN
2. PH due to left-sided heart disease
2.1 LV systolic dysfunction
2.2 LV diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathy
3. PH caused by lung disease or hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation syndromes
3.6 Long-term exposure to high altitudes
3.7 Developmental lung diseases
4. Chronic thromboembolic disease
5. PH with unclear or multifactorial mechanisms
5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

APAH indicates pulmonary arterial hypertension associated with other disease; CHD, congenital heart disease; CTD, connective tissue; LV, left ventricular; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary veno-occlusive disease; and WHO, World Health Organization.

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3. Diagnostics: Assessment and Monitoring

As a result of disease complexity and the importance of experience with specific diagnostic procedures and therapeutic strategies, the evaluation and care of pediatric PH patients should be provided or comanaged by specialty PH centers that include comprehensive, multidisciplinary medical subspecialists, nursing, and social work expertise. Routine follow-up visits should be performed, at a minimum, every 3 to 6 months, with more frequent visits for patients with advanced disease or after initiation of or changes in therapy. Those comanaged should be seen, at a minimum, biannually by or in consultation with PH specialty centers. At the time of initial PH diagnosis, a comprehensive history and physical examination, combined with diagnostic testing for the assessment of PH pathogenesis/classification and formal assessment of cardiac function, should be performed (Figure 1 and Table 6). Specifically, a chest x-ray, ECG, echocardiogram, chest computed tomography (CT) with and without contrast, 6MWD test, laboratory studies including BNP, and cardiac catheterization should be considered critical components of a thorough evaluation.[12] Other tests such as a sleep study, CPET, additional laboratory work, MRI, and lung perfusion scans may have greater value in select populations.

3.1. Echocardiography

Echocardiography is the noninvasive test of choice for initial screening for PH. It is useful for identifying potential causes of PH, evaluating RV function, and assessing related comorbidities.[13] In CHD-associated PH, increased pulmonary pressures can be due to high pulmonary blood flow or postcapillary pressures, necessitating careful assessment of cardiac anatomy and evaluation for associated lesions to correctly diagnose and manage PH. Intracardiac and extracardiac shunts such as ASD, VSD, PDA, and aortopulmonary window can be diagnosed, and the severity and direction of shunt can be assessed. Left-sided obstructive lesions, including pulmonary venous obstruction, cor triatriatum, mitral stenosis, small LV, LV outflow tract and aortic valve obstruction, and coarctation of the aorta, should also be ruled out. After a comprehensive initial evaluation, echocardiograms using PH-specific protocols should be performed on average every 4 to 6 months in case of disease progression or a change in therapy.

3.1.1. Estimates of PAP and PVR

Determination of PAP by Doppler echocardiography is central to patient screening and evaluation. The velocity of the tricuspid regurgitation (TR) jet, when adequate, should be recorded to assess RV systolic pressure, which, in the absence of RV

Table 5. Classification of Pediatric PHVDs (Panama): General Categories

Prenatal or developmental PH vascular disease
Perinatal pulmonary vascular maladaptation
Pediatric cardiovascular disease
Bronchopulmonary dysplasia
Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
Pediatric lung disease
Pediatric thromboembolic disease
Pediatric hypobaric hypoxic exposure
Pediatric pulmonary vascular diseases associated with other system disorders

PAH indicates pulmonary arterial hypertension; and PHVD, pulmonary hypertensive vascular disease.

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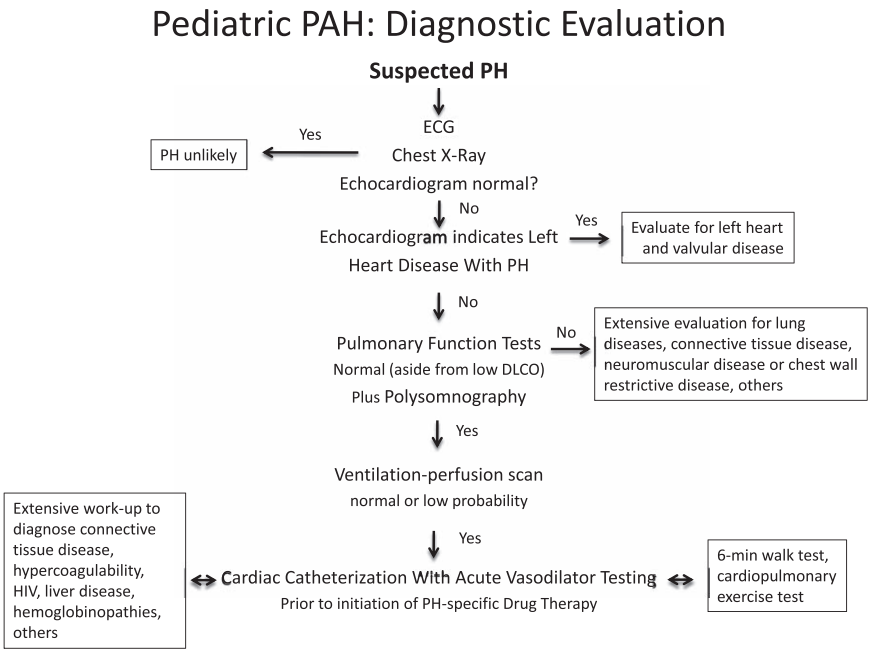

Figure 1. Algorithm illustrating general diagnostic workup for pediatric pulmonary arterial hypertension. DLCO indicates carbon monoxide–diffusing capacity; and PH, pulmonary hypertension.

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outflow obstruction, reflects systolic PAP.[14,15] The TR jet may be inadequate to determine peak velocity in 10% to 25% of PH patients, making assessment difficult.[16] When weak, the TR Doppler signal can be enhanced by the use of agitated saline. Although commercially available, echo contrast agents are not currently approved for use in children.[17,18] The Doppler beam should be aligned parallel to the TR jet. Multiple transducer positions should be used to record the highest velocity to reduce the underestimation of the TR velocity.[19] Systemic blood pressure should be recorded with each echocardiogram, especially in young infants, to document the ratio of pulmonary artery to systemic arterial pressure.

Because the TR jet represents the pressure gradient between the RV and right atrium (RA), RA pressures should be added to correctly quantify RV systolic pressure. RA pressure can be estimated by a variety of methods, such as including the degree of inferior vena cava collapsibility during respiration.[20–26] If RV systolic pressure is high, RA pressures are not necessary to diagnose PH. If TR velocities are borderline, cardiac catheterization may be necessary to determine PAP and PVR. The most important aspect of assessment of PAP by TR Doppler is an adequate and clear spectral Doppler profile. When the spectral display is adequate, the sensitivity of Doppler echocardiography is 0.79 to 1.0 and its specificity is 0.68 to 0.98 for the detection of PH in adults.[15,27,28] For pediatric patients in the setting of chronic lung disease, the sensitivity and specificity are lower.[29]

The position of the interventricular septum on 2-dimensional echocardiography can be useful to assess RV systolic pressures. Progressive leftward displacement and flattening of the interventricular septum occur in children when the RV systolic pressure is greater than half of systemic.[30,31] This septal flattening change can be quantified with the eccentricity index, which is calculated as the ratio of the LV minor and major axes in the short-axis view at the level of the mitral tendinous chords.[32] The LV eccentricity index not only predicts RV systolic pressures but also reflects RV- LV interactions in PH because leftward displacement of the interventricular septum impedes LV filling. The position of the interventricular septum should be noted in every examination even if the eccentricity index is not formally calculated.

Because PAP and pulmonary blood flow can be estimated by Doppler echocardiography, it is possible to estimate PVR.[33–36] These indirect measures have not been validated with sufficient patient numbers, and questions about accuracy persist. Consequently, catheterization-derived measurement of PVR is still required. Shortening of the PA acceleration time and midsystolic notching of the PA Doppler signal suggest the presence of PH. However, PA notching is not always related to the severity of PH and can be intermittent because it is determined by complex interactions between pulmonary resistance, elastance, and wave reflection.[37] Similarly, the RV pre-ejection period (the time between QRS onset and pulmonary flow onset) is related to PVR. The higher the PVR is, the longer the pre-ejection period is. Although proposed as a surrogate for PVR, the pre-ejection period may not be adequate as a basis for management decisions.[38]

3.1.2. Estimates of Ventricular Function

RV function and hypertrophy are important determinants of clinical status and outcomes. RV functional assessment by echocardiogram is complicated by difficult visualization of the RV (because of its anterior and retrosternal position), its nongeometric shape (which complicates simple modeling of volume and ejection fraction), and its prominent trabeculations.[39] Subjective assessment of RV function is common practice, but compared with MRI, its accuracy is low and inconsistent.[40,41] Because of its ubiquity and ease of use, however, subjective assessment of RV function continues to play a central role in PH diagnosis and management. Quantification of RV hypertrophy (RVH) is also difficult to measure and is largely a qualitative assessment.[42–44]

Two-dimensional echocardiography is recommended to assess RA enlargement[45] and the presence and severity of pericardial effusion.[46] RA size as a surrogate for RA pressure and pericardial effusions predict survival or the need for

Table 6. Laboratory Evaluation of Pediatric PH

General laboratory work
Complete blood count, platelet count
Urinalysis
Electrolytes, BUN, creatinine
BNP/NT-proBNP
Uric Acid
Cardiac studies
Echocardiogram
ECG
Cardiac catheterization
Cardiac MRI
Respiratory studies
Arterial blood gas
Chest x-ray
Chest CT
Pulmonary function tests
Ventilation/perfusion scan
Polysomnography
Coagulation studies
Factor VIII; factors II, V, and VII; factor V Leiden
Lupus anticoagulant
Protein C, protein S
β-2 Glycoprotein antibodies
Cardiolipin IgG, IgM antibody
Antithrombin III mutation
Platelet function assay
Portal hypertension
Liver function panel
Hepatitis screen
Abdominal/liver ultrasound
Thyroid panel (TSH, free T4, total T4)
CTD
ESR/CRP
ANA
Anti-DNA
Anti-cardiolipin antibodies
CH50 complement (C3, C4)
ANCA
Rheumatoid factor
HIV testing, toxins, drugs

ANA indicates antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibody; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; CRP, C-reactive protein; CT, computed tomography; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NT-proBNP, N-terminal probrain natriuretic peptide; and TSH, thyroid-stimulating hormone.

transplantation in adults with PH. Data on their prognostic significance in pediatric PH are inadequate.[47,48] The presence of an interatrial shunt and its direction should be noted as indicators of RV compliance and RA pressure. A right-to-left shunt suggests decreased RV compliance and elevated RA pressures. RA volumes will be affected by TR, which should be recorded and its severity graded.

RV dilation is an early sign of RV dysfunction in PAH,[49] as described in recent guidelines.[48] Two-dimensional linear measurements have limited correlation with RV volumes as measured by MRI but can be useful for serial evaluation in individual patients.[50,51] Three-dimensional echocardiography, using 2-dimensional knowledge-based reconstruction or semi-automated border detection, can quantify RV volumes and ejection fraction with good accuracy and reproducibility compared with MRI.[52–56] Three-dimensional echocardiography can also be used to assess RV volumes and ejection fraction in patients with CHD and those with single-ventricle physiology, although 3-dimensional echocardiography tends to underestimate volumes compared with MRI.[56–61] RV 3-dimensional echocardiography has been assessed in adults with PAH,[62,63] but there are limited availability and insufficient data on 3-dimensional echocardiography in pediatric PAH to recommend its routine use. LV function is an important prognostic factor in adults with PAH,[64] and LV hemodynamic parameters may be useful to assess infants with PPHN.[65]

3.1.3. Longitudinal Global and Regional Function

RV contraction is predominantly longitudinal in normal function and in PAH.[66–70] Assessment of longitudinal RV lateral wall performance can be performed through M-mode, 2-dimensional, tissue Doppler, and deformation imaging. Of these, tricuspid annular planar excursion (TAPSE) is most easily measured and accessible and has been evaluated in adult PAH.[71–73] TAPSE is obtained by placing an M-mode cursor through the lateral tricuspid annulus in the 4-chamber view and measuring annular excursion. In adults, TAPSE correlates with RV ejection fraction,[64] fractional area of change, RV stroke volume,[72] and survival.[72] Although normal TAPSE values have been established for children,[74] there are few pediatric data on its use in children with PAH. Likewise, interpretation of TAPSE should account for regional heterogeneity in that it may not reflect global RV function.[75,76]

3.2. Cardiac Catheterization

The general goals for cardiac catheterization in children with PH are (1) to confirm the diagnosis and assess the severity of disease; (2) to assess the response to pulmonary vasodilators (AVT) before starting therapy; (3) to evaluate the response to or the need for changes in therapy; (4) to exclude other, potentially treatable, diagnoses; (5) to assess operability as part of the assessment of patients with systemic to pulmonary artery shunts; and (6) to assist in the determination of suitability for heart or heart-lung transplantation. Catheterization should generally be performed at diagnosis before the initiation of PAH-targeted therapy. Exceptions may include critically ill patients requiring immediate initiation of advanced therapies. Catheterizations should be performed by pediatric catheterization teams experienced in PH to reduce related morbidity or mortality and to improve the quality of comprehensive studies.[77] In general, the study should include AVT (see below). Additionally, one should consider performing repeat cardiac catheterization in the setting of clinical worsening, 3 to 12

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months after a significant change in therapy, or every 1 to 2 years during follow-up.

3.2.1. Conduct of Cardiac Catheterization

An essential difference between cardiac catheterization in pediatrics and in adults is the need for either conscious sedation or general anesthesia in most children <15 years of age, depending on developmental stage. There is no clear consensus as to whether cardiac catheterization should be performed with general anesthesia or by sedation without tracheal intubation. The advantages of general anesthesia include a secure airway, a constant level of sedation, and control of blood gas status. Disadvantages include instability with induction, adverse effects of positive pressure ventilation on RV function, and alterations in pulmonary vascular hemodynamics that may not represent values while awake. Conscious sedation avoids the risks of induction and ventilation but may be associated with hypoxia and hypercarbia, particularly in children with airway obstruction, lung disease, and changing levels of sedation. It is essential that experienced teams undertake all cardiac catheterizations in children with PH. In these settings, the complication rates are 0% to 1%, risk of cardiac arrest is 0.8% to 2%, and risk of PHCs is 5%.[78–80]

Risk factors for adverse events include IPAH and suprasystemic PAP. Acute deterioration may occur during or after cardiac catheterization, and the availability of mechanical cardiopulmonary support in the event of deterioration is essential because resuscitation of pediatric patients with PH is poor by conventional techniques alone.[81] Close collaboration and case discussion between cardiologist and anesthesiologist are important.

Blood pH has a potent effect on the tone of the pulmonary vasculature of children.[82,83] Acidosis caused by hypercarbia or hypoperfusion is a powerful pulmonary vasoconstrictor, and alkalosis is a vasodilator.[84] Similarly, hypoxia causes vasoconstriction, whereas hyperoxia causes vasodilatation. Therefore, awareness of the arterial blood gas measurements during catheterization is critical for accurate interpretation of baseline hemodynamics and the response to acute pulmonary vasodilator testing. Drugs used for induction, sedation, and maintenance of anesthesia may also effect a change in pulmonary or systemic pressures and cause difficulty in the interpretation of results. Drugs with minimal effects on the PA pressure and PVRI in children include fentanyl,[85] ketamine,[86,87] and propofol.[88] Care must be taken to avoid systemic hypotension, particularly in patients with marked elevation of PAP with low cardiac output.

3.2.2. Hemodynamic Assessments: Oximetry

Ideally, oxygen saturation should be measured by an oximeter close to the cardiac catheterization laboratory. A "saturation run" is performed to determine the presence of a cardiac shunt. Sites sampled will be tailored to the clinical situation. In some cases in which there is difficulty obtaining a true pulmonary artery saturation sample (eg, multiple sources of pulmonary blood flow), pulmonary blood flow calculation by MRI beforehand or simultaneously with cardiac catheterization may be useful for the calculation of PVRI. With right-to-left shunting or pulmonary venous desaturation, it is important to sample the pulmonary veins, left atrium (LA), and LV, as well as the ascending and descending aorta. Arterial blood gases should be reviewed frequently during each study.

3.2.3. Pressure Measurements

Because great reliance is placed on the pressure recordings, it is essential that pressure measurements are taken at end expiration if the patient is breathing spontaneously and at end inspiration if ventilated. Pressures measured include RA, RV, PA (proximal and distal if PA stenoses are suspected), LA, PA wedge, and systemic artery pressures. Difficulty in obtaining an accurate wedge pressure indicative of LA pressure is common and applies no less to children than to adults.[89] If the wedge pressures are unusually high or low, it is prudent to measure LV end-diastolic pressure simultaneously with the wedge pressure. In cases when there is suspected obstruction between pulmonary artery and LV, it is important to measure PA wedge pressure, pulmonary vein pressure, LA pressure, and LV end-diastolic pressure.

3.2.4. Measurement of Systemic and Pulmonary Blood Flow

Measurements of pulmonary and systemic (cardiac index) blood flow are required to calculate PVRI and SVR index, and cardiac index is an important predictor of outcomes. It is essential in the evaluation of patients with PH with a shunt lesion or disease of the left side of the heart to determine whether the PH is associated with an elevated PVRI. Patients with high PAP but low PVRI (ie, PH in the absence of PVD) require different management.

Pulmonary blood flow can be reliably measured with the Fick principle.[90] The Achilles heel of this technique is the difficulty and expense of measuring oxygen consumption in clinical settings. However, the measurement of $\dot{V}o_2$ is crucial to obtaining accurate results, and a number of studies in children highlight the inaccuracies introduced by assuming $\dot{V}o_2$ from equations.[91–94] If measurement of $\dot{V}o_2$ is impossible, it has been suggested that using a number of different equations to predict $\dot{V}o_2$ and calculating a possible range of pulmonary blood flows are preferable.[95] Alternatively, use of the ratio of PVRI to SVR index yields a result that is unaffected by $\dot{V}o_2$, but the result will be affected by factors that alter SVR index out of proportion to PVRI. The Fick method is less accurate at high flows when the arteriovenous O_2 differences are small.

Thermodilution catheters are used to measure pulmonary blood flow or cardiac output if there are no intracardiac or extracardiac shunts and pulmonary and systemic blood flow can be assumed to be equal. Thermodilution may be inaccurate in the presence of low cardiac output or with severe tricuspid or pulmonary insufficiency.[96–100] However, in adults with PH, there is good correlation between the Fick equation and thermodilution in patients with severe TR or low cardiac output.[101] Thermodilution is the method of choice for measurement of cardiac output. The direct Fick equation with measured $\dot{V}o_2$ should be used if there are cardiac shunts or a difference of >10% to 15% on repeated thermodilution measurements.

3.2.5. Acute Vasoreactivity Testing

AVT in children is undertaken to assess the response of the pulmonary vascular bed to pulmonary-specific vasodilators. In children with IPAH or familial PAH (isolated PVHD), the result is used to define the likelihood of response to long-term

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treatment with CCB therapy and for prognosis. There are 2 definitions of responding to AVT in IPAH or isolated PHVD: (1) a decrease in mPAP of at least 10 mm Hg to <40 mm Hg with a normal or increase in CO[102–104] and (2) a decrease in mPAP ≥20%, an increase or no change in cardiac index, and a decrease or no change in PVR/SVR ratio.[1] There is controversy about the frequency of acute responders in pediatrics. The North American Registry to Evaluate Early- and Long-Term PAH Disease Management (REVEAL) data suggested that 30% to 50% were responders, whereas the UK[104,105] and Netherland registries[106] suggested that <10% of patients were acute responders, in keeping with adult data.

AVT in children with CHD is undertaken to assess whether the PVR will decrease sufficiently for surgical repair to be undertaken in borderline cases. The vast majority of children with CHD do not require cardiac catheterization as a prelude to repair. In general, positive AVT for borderline cases with posttricuspid shunts is defined as a decrease in PVRI to <6 to 8 WU·m^2 or PVR/SVR ratio <0.3.[107–110] However, AVT is only 1 measure used to define operability, and the whole clinical picture, the age of the patient, and the type of lesion need to be taken into consideration.

AVT may be studied with iNO (20–80 ppm), 100% oxygen, inhaled or intravenous PGI_2 analogs, or intravenous adenosine or sildenafil.[109,111–114] Some studies suggest a synergy between iNO and a high inspired oxygen concentration.[109,111,115] Testing with 100% oxygen in children with CHD has been criticized because oxygen consumption cannot be measured simultaneously and the arteriovenous O_2 difference becomes very small, which increases errors in the calculation of pulmonary blood flow.[116] Temporary balloon occlusion of a PDA, an ASD, or less often a VSD may be undertaken to assess whether permanent occlusion would be beneficial and have implications for the potential role for PAH-specific drug therapy. A decrease in PAP with temporary occlusion may indicate suitability for permanent shunt occlusion.[117]

Cardiac catheterization may be performed to assess the suitability for heart transplantation alone versus heart and lung transplantation in select children.[118] Patients with increased LA pressures may have an increased calculated PVR because the cardiac index is low, the pulmonary vasculature is constricted, or there is an element of PVD with a reduction in recruitable vessels. In general, a PVRI <8 WU·m^2 and transpulmonary gradient <15 mm Hg either at baseline or with acute reactivity testing are indications that heart transplantation alone may be undertaken. Specific pulmonary vasodilators may increase LA pressure and precipitate pulmonary edema if the cardiac output of these patients cannot be increased. Importantly, acute vasodilators may rapidly induce severe pulmonary edema in patients with normal PA wedge and LA pressures who have PVOD, requiring close monitoring in anticipation of this potential adverse event.

3.3. Other Imaging Studies

3.3.1. Computed Tomography

CT may yield valuable information on disease pathogenesis in patients undergoing evaluation for PH. Standardized protocols consist of high-resolution CT images of the lung parenchyma with CT angiography to aid in the assessment of interstitial lung disease, PVOD, vascular malformations, or other vascular lesions. CT signs of chronic thromboembolic disease include the absence or a sudden loss of contrast-filled vessels and "mosaic perfusion," which reflects the inhomogeneity of lung perfusion. CT evidence of PVOD includes lymph node enlargement, centrilobular ground-glass opacities, and septal thickening with pulmonary artery enlargement. In contrast, CT signs of pulmonary capillary hemangiomatosis include smooth interlobular septal thickening, diffuse multifocal regions of ground-glass opacity, pleural effusions, and enlarged central pulmonary arteries. CT angiograms are now the gold standard for detecting pulmonary embolism in both pediatric and adult populations.[119,120] Because smaller children tolerate the chest CT angiogram better than the ventilation/perfusion scan, many centers prefer CT scans in lieu of ventilation/perfusion studies. Implementation of radiation dose reduction protocols for CT scans is also an important factor.[121] In adults, the ventilation/perfusion scan is more sensitive for the diagnosis of chronic pulmonary embolism than CT angiography, but there are inadequate data for a strong recommendation in children.

3.3.2. Ventilation/Perfusion Scan

The ventilation/perfusion scan is commonly used to assess ventilation-perfusion mismatch owing to airway or vascular obstruction and has been useful in determining the presence of pulmonary embolism, determining asymmetrical blood supply after surgical repair of obstructed pulmonary arteries, and assessing abnormal chest radiograph findings. Ventilation/perfusion scans require that a child be motionless for several minutes after the inhalation of a radioisotope and the injection of radioisotope-tagged albumin. Some centers use only the perfusion portion of this study to limit the need for patient cooperation. The need for sedation to guarantee cooperation with the ventilation portion of the study carries its own risks. Ventilation/perfusion scans are increasingly supplanted by CT angiography in pediatric patients.

3.3.3. Magnetic Resonance Imaging

Despite enormous progress in quantitative echocardiography, cardiac MRI remains the gold standard for evaluating the RV. Low interstudy and interobserver variability makes it reliable for serial studies. However, for frequent, serial assessments, echocardiography is preferred.[122–126] The most common use for MRI in pediatric PH patients is to assess RV size, mass, and function in the initial evaluation and during follow-up. Cardiac MRI is also used to quantify biventricular volumes and pulmonary blood flow, to assess cardiopulmonary anatomy, and to determine pulmonary artery mechanical properties. Several cardiac MRI–derived parameters predict morbidity and mortality in PH associated with CHD.[127,128] Ventricular end-diastolic volumes, stroke volume, and RV ejection fractions predict mortality adults with PAH.[129] However, these end points require further validation in pediatric populations. Invasive pulmonary angiography remains useful for imaging the pulmonary vasculature. However, because exclusion of thrombi is an essential part of the PAH evaluation, magnetic resonance angiography may be an efficient and potentially cheaper alternative.[130]

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3.4. Physiological Assessments

3.4.1. 6MWD Test

Although some data are available, normative values of 6MWD for age, sex, and leg length have not been well standardized in children.[131] Within similar functional classes, children walk farther in 6 minutes than adults, likely because of differences in the dynamics of the right side of the heart and level of general conditioning. There are no data to support the use of 6MWD to predict survival in pediatric PH. Most practitioners use changes in serial 6MWD for longitudinal follow-up.

3.4.2. Cardiopulmonary Exercise Testing

CPET is frequently used to evaluate and follow up patients with PH. Standardization of the pediatric CPET has been difficult,[132–134] and studies have suggested that CPET in adults does not correlate with quality of life or mortality risk, preventing its widespread adoption as a clinical end point in clinical trials.[135] Pediatric CPET using the bicycle ergometer is usually possible in children >7 years of age, and younger children may be able to perform CPET on a treadmill. Heart rate and rhythm, oxygen saturation, and blood pressure are recorded in all subjects, and values at which the test will be halted are set a priori by clinical personnel. In the assessment of asymptomatic pediatric PH patients with CPET, the following variables are useful: maximal O_2 consumption, CO_2 elimination, maximal cardiac output, and anaerobic threshold. However, studies using pediatric CPET as a clinical end point are rare,[134] and additional work needs to be done to standardize pediatric CPET.

3.5. Biomarkers

BNP and its more stable byproduct, NT-proBNP, are released from the atria and ventricles in response to volume overload and stretch. BNP levels are inversely proportional to prognosis in PH.[136–138] BNP and NT-proBNP are not specific markers for mechanisms of pulmonary vascular or RV remodeling but are markers that increase with atrial dilatation or failure of either ventricle.[136] In patients with an unrepaired VSD and Eisenmenger complex in whom the RV has been pressure loaded from birth (when there is no heart failure), BNP can remain within the normal range despite profound cyanosis from suprasystemic PVR. In this setting, BNP increases only when the LV starts to dilate and fail. BNP has a shorter half-life than NT-proBNP but varies less with renal function. BNP values can be used to monitor response to therapy. BNP levels decrease as RV function improves with therapy. In the adult, normal values are <100 pg/mL, but in children, the true normal range is currently uncertain. Several small studies suggest that the normal value is highest just after birth, falls to <50 pg/mL by 6 to 9 months of age, and rises to adult levels during late adolescence. Problems with sample handling and different assay characteristics for BNP and pro-BNP can alter measurements, and the absolute value has less significance than the trend.[138–144] As in adult PAH, increased levels of atrial natriuretic peptide, troponin T,[145] and uric acid[146,147] correlate with poor short-term outcome in older children and adolescents.[148]

Recommendations

1. **At the time of initial PH diagnosis, a comprehensive history and physical examination combined with diagnostic testing for the assessment of PH pathogenesis/classification and formal assessment of cardiac function should be performed before the initiation of therapy at an experienced center (*Class I; Level of Evidence B*).**
2. **Imaging to diagnose pulmonary thromboembolic disease, peripheral pulmonary artery stenosis, pulmonary vein stenosis, PVOD, and parenchymal lung disease should be performed at the time of diagnosis (*Class I; Level of Evidence B*).**
3. **After a comprehensive initial evaluation, serial echocardiograms should be performed. More frequent echocardiograms are recommended in the setting of changes in therapy or clinical condition (*Class I; Level of Evidence B*).**
4. **Cardiac catheterization is recommended before initiation of PAH-targeted therapy (*Class I; Level of Evidence B*). Exceptions may include critically ill patients requiring immediate initiation of empirical therapy (*Class I; Level of Evidence B*).**
5. **Cardiac catheterization should include AVT unless there is a specific contraindication (*Class I; Level of Evidence A*).**
6. **The minimal hemodynamic change that defines a positive response to AVT for children should be considered as a ≥20% decrease in PAP and PVR/SVR without a decrease in cardiac output (*Class I; Level of Evidence B*).**
7. **Repeat cardiac catheterization is recommended within 3 to 12 months after the initiation of therapy to evaluate response or with clinical worsening (*Class I; Level of Evidence B*).**
8. **Serial cardiac catheterizations with AVT are recommended in the following situations:**
   a. **Serial cardiac catheterizations are recommended during follow-up to assess prognosis and potential changes in therapy (*Class I; Level of Evidence B*).**
   b. **Intervals for repeat catheterizations should be based on clinical judgment but include worsening clinical course or failure to improve during treatment (*Class I; Level of Evidence B*).**
9. **MRI can be useful as part of the diagnostic evaluation and during follow-up to assess changes in ventricular function and chamber dimensions (*Class IIa; Level of Evidence B*).**
10. **BNP or NT-proBNP should be measured at diagnosis and during follow-up to supplement clinical decisions (*Class I; Level of Evidence B*).**
11. **The 6MWD test should be used to follow exercise tolerance in pediatric PH patients of appropriate age (*Class I; Level of Evidence A*).**
12. **A sleep study is recommended in the following situations:**
    a. **Should be part of the diagnostic evaluation of patients with PH at risk for sleep-disordered breathing (*Class I; Level of Evidence B*).**
    b. **Is indicated in the evaluation of patients with poor responsiveness to PAH-targeted therapies (*Class I; Level of Evidence B*).**

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4. Genetics

Familial cases of PAH have been long recognized[149] and are usually inherited in an autosomal-dominant fashion. The most recent PH classification replaces familial PAH with the term HPAH at least in part to recognize the fact that 10% to 40% of cases previously thought to be IPAH harbor identifiable mutations in bone morphogenetic protein receptor II gene (*BMPR2*) and therefore pose a hereditary risk to other family members. Only 6% of PAH patients reported a family history of PAH in the prospective National Institutes of Health registry.[150] However, a family history of PAH may go unrecognized in IPAH cases with *BMPR2* mutations as a consequence of undiagnosed disease, incomplete penetrance, or de novo (spontaneous) mutations.

Two groups independently and simultaneously identified *BMPR2* as the primary pulmonary hypertension gene.[151] A mutation in *BMPR2* can be identified in ≈70% of HPAH and ≈10% to 40% of IPAH cases.[152–154] *BMPR2* is a member of the transforming growth factor-β receptor superfamily. Other members of this family are also recognized as uncommon causes of HPAH. Heterozygous germline mutations in activin-like kinase-type i (*ALK1*)[155] and endoglin (*ENG*)[156] cause hereditary hemorrhagic telangiectasia (HHT) and may rarely lead to the development of PAH. *SMAD8* has also been recognized recently as a possible cause of PAH.[157] Moreover, mutations in the *SMAD4* gene have been linked to HHT and juvenile polyposis and HHT.[158,159] The genetics of PAH are complex because of the incomplete penetrance. The majority of families with HPAH have mutations in *BMPR2* that are autosomal-dominantly inherited. However, the penetrance of the mutation is low, with an estimated lifetime risk of 10% to 20%.[160,161] The disease is more frequent in adult women, with a female:male ratio ranging from 2:1 to 4:1.[162,163] Ongoing studies continue to identify novel genetic factors that are associated with familial forms of PAH, including *BMPR2*, *ALK1*, *ENG*, *SMAD8*, *Cav1*, *KCNK3*, and *ELF2AK4*.

Both incomplete penetrance and the significantly skewed sex ratio only after puberty suggest that the *BMPR2* mutation alone may not be sufficient to cause PAH. A "second hit," which may include other genetic or environmental modifiers of *BMPR2*, may be necessary to induce the development of PAH. Heterozygous *BMPR2* sequence variants have been identified in a small subset of patients with PAH associated with (relatively brief) exposure to fenfluramine,[164] CHD,[165] and veno-occlusive disease,[166] raising the question of whether such factors represent disease triggers in the face of inherited susceptibility in some patients. *BMPR2* mutations have not previously been identified in modestly sized series of PAH associated with the scleroderma-spectrum disease, HIV,[167] Down syndrome, neurofibromatosis-1,[168] Gaucher disease,[169] or autoimmune polyendocrine syndrome.[170]

HPAH resulting from *BMPR2* mutations is associated with an earlier age of onset and a slightly more severe hemodynamic impairment at diagnosis: Patients with HPAH had higher mPAP, lower cardiac index, and higher PVR than patients with IPAH but interestingly had similar survival, although they were more likely to be treated with parenteral PGI_2 therapy or lung transplantation.[171] Both children and adults with PAH and *BMPR2* mutations are, however, less likely to respond to acute vasodilator testing and are unlikely to benefit from treatment with CCBs.[172,173] Symptomatic HPAH patients carrying *ALK1* mutations, most without HHT, have an earlier age of onset and more rapid disease progression than HPAH patients with *BMPR2* mutations despite responsiveness to vasodilators at the time of diagnosis.[174]

4.1. Genetic Testing for PAH

Clinical genetic testing continues to expand but is currently available for evaluating PAH related to *BMPR2*, *ALK1*, *ENG*, and other genes (Table 7). Genetic testing is often considered in pediatric PAH to explain the origin of the disease and to counsel family members about identifying other family members at risk and accurately determining the risk of recurrence in future children. Genetic testing offers not only diagnostic information for the patient but also potentially valuable information for the family. In most cases, genetic analysis will begin with analysis of *BMPR2* unless there are specific clinical symptoms or family history to suggest HHT such as mucocutaneous telangiectasias, recurrent epistaxis, gastrointestinal bleeding, or arteriovenous malformations in the pulmonary, hepatic, gastrointestinal, or cerebral circulations. Crude indirect estimates of the population carrier frequency for *BMPR2* mutations range from 0.001% to 0.01%.[175]

At this time, many PAH experts do not routinely use genetic test results to guide the management of patients with PAH. Genetic testing can be offered to any individual with a family history of PAH or IPAH (without other known affected family members), and physicians may have a duty to inform these patients of the possibility that PAH could develop in other family members. It is always best to start genetic testing with a family member who has the diagnosis of PAH to determine whether he or she carries a *BMPR2* mutation and to determine the specific familial *BMPR2* mutation.

A negative genetic test result in an unaffected family member is uninformative and could be the result of a familial mutation in another gene besides *BMPR2* , a mutation in *BMPR2* not detected by the assay performed, or a family member who is truly negative and at no risk for PAH in a family segregating a *BMPR2* mutation. This can provide psychological relief to patients and parents of children at risk for HPAH. Conversely, identifying a *BMPR2* mutation in a child with PAH without a family history can cause significant anxiety to family members when they realize that there is an increased risk for members

Table 7. Genetics of PAH

Gene Name	Clinical Correlates
BMPR2	≥75% of HPAH cases
ACVRL1 or *ALK1*	PAH associated with HHT
ENG	PAH associated with HHT
SMAD9, *SMAD4*, or *SMAD8*	Downstream signals of TGF-β
CAV1	Disruption of caveolar formation
KCNK3	Encodes K^+ channel protein
EIF2AK4 (*GCN2*)	PVOD and PCH

HHT indicates hereditary hemorrhagic telangiectasia; HPAH, heritable pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease; and TGF-β, transforming growth factor-β.

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of the family and that disease symptoms can begin at any age. The most commonly cited reason for genetic testing for PAH is to provide information to and about children.[176]

Clinical genetic testing is available in North America and Europe, with the current cost of testing ranging from approximately US $1000 to $3000 to analyze the first member of a family. Once the mutation in a family is known, testing other family members for a family-specific mutation costs US $300 to $500. Genetic testing should involve pretest and posttest genetic counseling with a genetic counselor experienced in PH.

Genetic counseling should be performed before genetic testing for PAH to address the complex issues of incomplete penetrance, questions of surveillance for genetically at-risk family members, reproductive questions, concerns about genetic discrimination, and the psychosocial issues of guilt and blame that accompany genetically based diseases. Such genetic services can be provided either by PAH care providers with experience in genetic testing or by genetic professionals (geneticists and genetic counselors) with experience in PAH. Often, these services may be available only at PAH centers of excellence owing to the specialized nature of genetic testing for PAH. Families should be referred to a genetic counselor or a clinical geneticist to discuss reproductive options if a mutation is identified. It is important that, even if genetic testing is not performed, patients and families should be aware that there is an increased risk of PAH in any family with a history of PAH, and family members should be made aware of early signs and symptoms to ensure that a timely and appropriate diagnosis is made if other family members are affected in the future.

As a consequence of the incomplete penetrance and variable age of onset, identification of a *BMPR2* mutation may have a complex and serious psychosocial impact on the family and is often associated with feelings of guilt in the parent who has passed on mutations to the children. Genetic testing is most helpful when it can identify members of the family who are not genetically at risk for PAH and who can then forgo the otherwise recommended serial evaluations to screen for PAH.

The most common reasons for the pursuit of genetic testing are to inform children of their hereditary predisposition and to make informed decisions about family planning. Genetic testing is more commonly pursued in children than adults, especially if affected parents or parents of an affected child are concerned about the risk of recurrence and are considering having more children. In the past, many patients opted not to pursue genetic testing because of anxiety about genetic discrimination. Recognition of these concerns has led a number of countries to introduce either voluntary or legal codes to protect individuals requesting genetic counseling and formal testing. For example, in the United States, the Genetic Information Nondiscrimination Act, passed in May 2008, protects members of both individual and group health insurance plans from discrimination in coverage or cost of health insurance coverage and protects against discrimination in employment based on a genetic predisposition.[177] Genetic testing of children should be considered carefully because of the potential for significant psychological impacts on a child, particularly overt anxiety for the future development of a potentially fatal disease in the absence of currently known effective disease-prevention strategies.

4.2 Clinical Monitoring of Individuals at Risk

Clinical monitoring of patients with a family history of PAH or carriers of the *BMPR2* mutation has not been evaluated rigorously. Consideration has been given to regular surveillance every 1 to 5 years by clinical examination, echocardiogram,[13] exercise stress echocardiography, and echocardiogram with hypoxia.[178] A great challenge in studying the natural history and disease progression of PAH is the availability of a sensitive, noninvasive means of measuring PAP. Echocardiogram is a relatively insensitive tool in the early stages of the disease. Provocation such as exercise or hypoxemic conditions would likely increase the sensitivity of an echocardiogram. Catheterization of the right side of the heart at rest and with exercise should be more sensitive than echocardiogram but carries the risks of an invasive procedure and is not indicated for surveillance. Pharmacological provocation could be used to demonstrate abnormal pulmonary vasoreactivity. The 1998 World Pulmonary Hypertension Conference suggested that first-degree relatives of known HPAH patients should be screened annually through clinical examination and echocardiography.[179] It is hoped that with regular surveillance individuals can be diagnosed earlier in their disease and benefit from early treatment. Although there are currently no data to suggest that early diagnosis will improve outcome, such studies are in progress.

PAH is also associated with genetic syndromes with and without CHD, vascular disease, and hepatic disease (Table 8). Subjects with Down syndrome have an increased risk for PPHN and are more susceptible to PH with stresses such as CHD, upper airway obstruction, and OSA.[180,181] This increased risk for PH may reflect reduced alveolar surface area and loss of capillary surface area in Down syndrome.[182–184]

Recommendations

1. **Genetic testing with counseling can be useful for children with IPAH or in families with HPAH to define the disease origin, to identify family members at risk, and to inform family planning (*Class IIa; Level of Evidence C*).**
2. **Genetic testing of first-degree relatives of patients with monogenic forms of HPAH is recommended for the following:**
   a. **Genetic testing is indicated for risk stratification (*Class I; Level of Evidence B*).**
   b. **It is reasonable to screen asymptomatic carriers with serial echocardiograms or other noninvasive studies (*Class IIa; Level of Evidence B*).**
3. **Members of families afflicted with HPAH who develop new cardiorespiratory symptoms should be evaluated immediately for PAH (*Class I; Level of Evidence B*).**
4. **Families of patients with genetic syndromes associated with PH should be educated about the symptoms of PH and counseled to seek evaluation of the affected child should symptoms arise (*Class I; Level of Evidence B*).**

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Table 8. Genetic Syndromes Associated With an Increased Incidence of PH

PH with or without CHD
Down syndrome
DiGeorge syndrome
Scimitar syndrome
Noonan syndrome
Dursun syndrome
Cantu syndrome
PH without CHD
SCD
Adams-Oliver syndrome
Neurofibromatosis
Autoimmune polyendocrine syndrome
Gaucher disease
Glycogen storage disease I and III
Mitochondrial disorders (MELAS)

CHD indicates congenital heart disease; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; PH, pulmonary hypertension; and SCD, sickle cell disease.

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5. Persistent PH of the Newborn

At birth, the lung circulation must undergo a rapid and dramatic decrease in PVR to facilitate the 8-fold increase in pulmonary blood flow for successful transition to postnatal life. This decrease in PVR at birth is initiated by increased oxygen tension, the onset of ventilation, and vascular shear stress, which produces vasodilation through enhanced release of vasodilators such as NO and PGI_2. PPHN represents the failure to achieve and sustain the normal drop in PVR and the increase in pulmonary blood flow and oxygenation required for neonatal adaptation. Mechanisms that disrupt this process before birth resulting in PPHN remain incompletely understood. PPHN complicates many neonatal cardiopulmonary diseases and should be considered a possible cause of neonatal cyanosis. Timely recognition and therapy are important because PPHN is associated with high rates of neonatal mortality and morbidity, including significant neurodevelopmental sequelae. The prevalence of PPHN has been estimated at 1.9 per 1000 live births,[185] but this estimate is based on a study of infants referred to level III neonatal intensive care units requiring mechanical ventilation and other advanced therapies.[186] Before the advent of ECMO, PPHN was associated with >50% mortality. Even with precise diagnosis, the availability of specific pulmonary vasodilators such as iNO, and extracorporeal support, early mortality for PPHN remains 8% to 10%. Long-term outcomes for PPHN include high rates of neurodevelopmental impairment at 18 months of age, as defined by mental developmental index <70, cerebral palsy, deafness, and blindness.[187,188]

Unlike PAH in older populations, PPHN is rarely familial, and few genetic causes have been identified. PPHN often complicates developmental lung diseases, including Down syndrome, ACD, genetic abnormalities of surfactant function, and lung hypoplasia in diverse settings.[184,189] Higher rates of PPHN have been observed after maternal use of salicylates or selective serotonin reuptake inhibitors late in pregnancy,[190–194] although the association with maternal selective serotonin reuptake inhibitor use remains controversial. Delivery before 39 weeks of gestation is now appreciated as being strongly associated with worse neonatal outcomes, in large part because of an elevated incidence of neonatal respiratory failure.[195,196] Evidence suggests that up to 2% of all preterm infants will have early acute PPHN, particularly after prolonged preterm rupture of membranes or oligohydramnios.[197,198] Moreover, severe PPHN requiring ECMO support is more prevalent in late-preterm and early-term infants than in full-term infants.[199]

5.1. Clinical Diagnosis and Therapy

Clinical manifestations of PPHN include labile oxygenation, differential saturation (higher Spo_2 in the right upper extremity compared with a lower extremity), or profound hypoxemia despite oxygen and mechanical ventilation. These findings are not specific for PPHN, and echocardiography is required to exclude CHD and thus establish the diagnosis of PPHN. Echocardiography also determines whether LV dysfunction is present, which is important because it can produce pulmonary venous hypertension that would potentially be aggravated by a pulmonary vasodilator.

5.2. General Care

Treatment of PPHN includes optimization of lung volume and function, oxygen delivery, and support of cardiac function. Systemic blood pressure should be maintained at normal levels for age with volume and cardiotonic therapy, with the primary goal of reducing both LV and RV dysfunction and enhancing systemic O_2 transport. Increasing blood pressure to supraphysiological levels for the sole purpose of driving a left-to-right shunt across the PDA may transiently improve oxygenation but will not reduce PVR and should be avoided.

High oxygen concentrations are commonly used to reverse hypoxemia and hypoxic pulmonary vasoconstriction in infants with PPHN. However, extreme hyperoxia (Fio_2 >0.6) may be ineffective owing to extrapulmonary shunt and may aggravate lung injury.

Poor lung expansion will exacerbate PPHN and may be reversed with high-frequency ventilation, although lung overexpansion should be avoided. Exogenous surfactant may improve lung expansion and reverse PPHN, particularly in infants with meconium aspiration syndrome or other significant parenchymal disease.[200,201] However, surfactant did not reduce ECMO use in newborns with idiopathic PPHN and carries a risk for acute airway obstruction.[201] Therefore, the use of surfactant should be considered only for infants with severe parenchymal lung disease and poor lung recruitment. In some cases, lung recruitment may be sufficient to lower PVR without the need for PH-specific therapy or may enhance responsiveness to iNO.[202]

Acidosis can induce pulmonary vasoconstriction and should be avoided. Forced alkalosis induced by hyperventilation or infusion of sodium bicarbonate was frequently used before the approval of iNO.[185] Although transient improvements in Pao_2 may be observed in the short term, no studies have demonstrated long-term benefit. Prolonged alkalosis may

paradoxically worsen pulmonary vascular tone, reactivity, and permeability edema[203] and may produce cerebral constriction, reduced cerebral blood flow, and worse neurodevelopmental outcomes.

Infants with sustained hypoxemia or compromised hemodynamic function should be considered for ECMO at a center that is equipped with appropriate equipment and experienced personnel.[204] The oxygenation index is a useful gauge for judging the severity of disease. The oxygenation index is calculated as follows: (mean airway pressure×Fio_2×100)/Pao_2. An oxygenation index >40 is an indication to consider referral to an ECMO center.

5.3. Pulmonary Vasodilator Therapy

iNO is approved by the US Food and Drug Administration (FDA) as specific pulmonary vasodilator therapy for PPHN in near-term and term infants. Its use is based on extensive safety and efficacy data obtained from large placebo-controlled trials. iNO acutely improves oxygenation and decreases the need for ECMO support in newborns with PPHN and an oxygenation index >25. However, up to 30% to 40% of infants do not achieve a sustained improvement in oxygenation with iNO, and iNO does not reduce mortality or length of hospitalization. Doses of iNO >20 ppm do not enhance oxygenation or other outcomes and will increase the risk of methemoglobinemia and other complications. One clinical trial that enrolled infants with an earlier stage of respiratory failure (oxygenation index, 15–25) found that iNO did not decrease the incidence of ECMO or death or improve other patient outcomes, including the incidence of chronic lung disease or neurodevelopmental impairment. On the other hand, a smaller single-center study suggested that delaying iNO initiation until respiratory failure is advanced (oxygenation index of >40) could increase the length of time on oxygen.[205]

The most important criterion for starting iNO is a diagnosis of PPHN with extrapulmonary right-to-left shunting as established by echocardiography. There is less evidence to guide optimal weaning procedures. Once oxygenation improves, iNO can usually be weaned relatively rapidly to 5 ppm without difficulty and discontinued within 5 days.[206] Infants who remain hypoxemic with evidence of PPHN beyond 5 days are more likely to have an underlying cause of dysregulated pulmonary vascular tone such as ACD,[189] severe lung hypoplasia, or progressive lung injury. When iNO is stopped abruptly, rebound PH may develop, even if no improvement in oxygenation was observed at the onset of therapy.[207] This phenomenon can lead to life-threatening elevations of PVR and decreased oxygenation (PHCs)[208,209] but can often be overcome by weaning iNO to 1 ppm before its discontinuation. Although not recommended for the prevention of chronic lung disease in preterm infants (BPD),[210] several series have shown improved oxygenation and pulmonary hemodynamics in preterm infants with PPHN physiology, especially in the setting of oligohydramnios and growth restriction.[211–213]

A small RCT with oral sildenafil showed improved oxygenation and survival in PPHN.[214] Likewise, an open-label pilot trial demonstrated that continuous intravenous infusion of sildenafil improved oxygenation in infants with PPHN, including those who were not receiving iNO.[215] Sildenafil clearance in the early neonatal period is low as a result of the relative immaturity of the hepatic cytochrome P450 system but rapidly increases during the first week of life.[216] Hypotension can occur during the initial loading infusion but was not observed when the loading dose (0.4 mg/kg) was delivered over 3 hours, followed by a maintenance dose of 1.6 $mg \cdot kg^{-1} \cdot d^{-1}$.

Systemic administration of PGI_2 is commonly used for PAH in children and adults but is rarely used in neonates because of the risk of systemic hypotension or ventilation-perfusion mismatch. In infants who are poorly responsive to iNO, inhaled PGI_2 can transiently elicit pulmonary vasodilation[217–219] and enhance oxygenation.[220] However, the alkaline solution needed to maintain drug stability can irritate the airway, and precise dosing can be difficult because of loss of medication into the nebulization circuit. Further investigations should focus on preparations that are better suited for airway delivery such as iloprost or treprostinil. These preparations are more stable than PGI_2 and have longer half-lives that allow intermittent dosing with ultrasonic nebulizers. Intravenous milrinone may also facilitate PPHN treatment by enhancing myocardial performance or lowering SVR in the setting of LV dysfunction.

Plasma ET-1 levels are increased in infants with PPHN and correlate with the severity of illness.[221,222] ET blockade enhances pulmonary vasodilation in experimental PPHN,[223] and recent case reports suggest that the ERA bosentan may improve oxygenation in neonates with PPHN.[224,225] However, clinical data do not currently support its use in PPHN.

Recommendations

1. **iNO is indicated to reduce the need for ECMO support in term and near-term infants with PPHN or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (*Class I; Level of Evidence A*).**
2. **Lung recruitment strategies can improve the efficacy of iNO therapy and should be performed in patients with PPHN associated with parenchymal lung disease (*Class I; Level of Evidence B*).**
3. **ECMO support is indicated for term and near-term neonates with severe PH or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function (*Class I; Level of Evidence A*).**
4. **Evaluation for disorders of lung development such as ACD and genetic surfactant protein diseases is reasonable for infants with severe PPHN who fail to improve after vasodilator, lung recruitment, or ECMO therapy (*Class IIa; Level of Evidence B*).**
5. **Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to iNO, especially with an oxygenation index that exceeds 25 (*Class IIa; Level of Evidence B*).**
6. **Inhaled PGI_2 analogs may be considered as adjunctive therapy for infants with PPHN who are refractory to iNO and have an oxygenation index that exceeds 25 (*Class IIb; Level of Evidence B*).**
7. **Intravenous milrinone is reasonable in infants with PPHN and signs of LV dysfunction (*Class IIa; Level of Evidence B*).**

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8. **iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (*Class IIa; Level of Evidence B*).**

6. Congenital Diaphragmatic Hernia

CDH is a relatively rare disorder, occurring in 1 of every 2500 births, and is characterized by marked lung hypoplasia with PH and impaired cardiac performance. The presence of severe PH is a critical determinant of survival in infants with CDH, with high prevalence (63%) and mortality (45%).[226–229] PVR often remains at suprasystemic levels in newborns with CDH, causing right-to-left shunting across the foramen ovale and ductus arteriosus, resulting in profound hypoxemia. High PVR in CDH is due to vasoconstriction, pulmonary vascular remodeling, including decreased arterial density, and LV dysfunction.[230,231] PH contributes to poor outcomes in CDH during the immediate postnatal period, throughout the neonatal intensive care unit course, and during long-term follow-up throughout childhood.[230]

6.1. General Management of PH in CDH

Although cardiopulmonary management of CDH has undergone marked changes over the last 30 years, few of the interventions have been studied in RCTs. One of the most significant changes in management is timing of the operative repair. Initially considered a surgical emergency at birth, repair of the defect in the diaphragm is now usually done at least 24 hours after birth to provide time for stabilization of gas exchange and pulmonary and systemic hemodynamics. Two small RCTs have compared early (within 24 hours) and delayed (when stabilized) repair and reported that, although delaying operative repair is safe, there were no differences in mortality.[232]

The approach to mechanical ventilation in newborns with CDH is highly variable between centers and guided by little evidence. Severe lung hypoplasia increases susceptibility of the infant with CDH to acute lung injury and chronic lung disease, and minimizing ventilating volumes is critically important for reducing lung overdistention and improving outcomes. Lung protective strategies generally include the use of small tidal volumes during conventional ventilation and permissive hypercapnia. Alternatively, one can use high-frequency oscillatory ventilation.[233] Permissive hypercapnia has been widely adopted and is thought to improve outcomes.

However, interpretation of the mechanism of this benefit remains unclear owing to the concurrent use of selective pulmonary vasodilation and the elimination of aggressive hyperventilation to achieve respiratory alkalosis.[234,235] There have been no RCTs of permissive hypercapnia in infants with CDH, and RCTs of this strategy in premature infants have failed to show benefit in the reduction of chronic lung disease with the use of permissive hypercapnia.[236]

Current recommendations to reduce ventilator-induced lung injury in CDH include limiting peak inspiratory pressures during conventional mechanical ventilation to ≤25 cm H_2O, followed by treatment with high-frequency oscillatory ventilation if gas exchange is inadequate.[237,238] This strategy minimizes volutrauma and vascular injury.[239] Recognizing that functional residual capacity and total lung volume are reduced in infants with CDH, an initial target for delivered tidal volumes is roughly 3.5 to 5 mL/kg. Clinical trials have shown that high-frequency oscillatory ventilation is a useful adjunct in the management of severe CDH when used as rescue therapy for infants failing conventional ventilation.[240,241]

6.2. PAH-Specific Therapy

Severe PH complicates the course of most infants with CDH, but the management of PH in CDH remains controversial. Because RCTs have shown that iNO reduced the need for rescue therapy with ECMO in many newborns with PPHN,[206,242,243] iNO was considered a promising therapy for the treatment of acute PH in CDH.[244] Early reports demonstrated that iNO can improve oxygenation and PH in some infants with severe CDH shortly after birth.[244,245] However, 2 RCTS of iNO treatment in the first hours after birth for CDH have been reported,[206,246] showing that early iNO treatment in patients with CDH had no effect on the combined end point of death and ECMO use.[206,246] In 1 trial, ECMO use was significantly higher in the iNO-treated group. Failure of iNO to cause sustained improvement in newborns with CDH may be due partly to the complicating LV pathology in CDH (LV systolic and diastolic dysfunction and small LV size).[247] Lowering PVR and increasing preload to an abnormal LV that cannot respond to increased stroke volume may worsen pulmonary venous hypertension and cause pulmonary edema. As a result, PAH-specific drug therapies should be used cautiously in newborns with CDH and PH. Some patients with CDH and severe LV dysfunction may benefit from augmenting the ability of the RV to maintain cardiac output through enhancement of right-to-left ductal shunting, which can be sustained by prostaglandin E_1 infusion to prevent ductal closure.

Patients with severe CDH may be poor responders to pulmonary vasodilation in the first 1 to 2 days after birth. However, iNO treatment may play an important role in stabilizing patients before ECMO is initiated, thus improving the chances that ECMO cannulation may proceed safely.[248] Overall, there is consensus that iNO therapy should not be used routinely in CDH; rather, its use should be limited to patients with suprasystemic PVR with right-to-left shunting across the oval foramen causing critical preductal hypoxemia and after optimal lung inflation and adequate LV performance are established.

Many drugs that can be delivered by inhalation have been reported in pilot studies as potential therapies for PH in CDH, including PGI_2, prostaglandin E_1, ethyl nitrite, sodium nitroprusside, and sodium nitrite[220,249–252]; however, none of these agents has been tested in controlled, clinical trials. Little is known about the inhalational toxicology of these drugs. Moreover, the LV dysfunction that characterizes severe CDH may limit the efficacy of pulmonary vasodilator drugs (as a class), as has been documented to occur with iNO. It is possible that the use of PDE inhibitors (eg, dipyridamole[253] and sildenafil[254]) may augment the pulmonary vasodilator effects of iNO in CDH.

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Although optimal therapy remains controversial, it is clear that PH portends poor prognosis and is associated with the need for prolonged mechanical ventilation, a second course of ECMO, or death.[228,255] In 1 study, 93% of infants achieving an estimated PAP of less than two-thirds systemic pressure by 2 weeks of age were discharged alive on room air.[221] Similarly, Dillon and colleagues[227] demonstrated 100% survival among infants with an estimated pulmonary/systemic arterial pressure ratio <0.5 by 3 weeks of age. In contrast, all infants with persistence of systemic levels of PAP at 6 weeks of age ultimately died. Some newborns with CDH may have persistent PH despite marked improvements in respiratory function, necessitating pulmonary vasodilator therapy to reduce PVR even when mechanical ventilation is no longer required. Overall, targeting late PH may be an effective approach to reducing mortality in a subset of newborns with CDH.[256] Resolution of PH during prolonged sildenafil therapy has been reported in CDH.[257,258] Management of chronic lung disease associated with CDH is similar to approaches used in subjects with BPD (see below).

Finally, PH can persist into infancy or childhood and may contribute to late morbidity and mortality in CDH patients. Infants with CDH require long-term follow-up that includes annual echocardiography, along with assessments of their overall respiratory course. Pulmonary arterial and venous structural abnormalities can contribute to late or sustained PH in infants with CDH and may be difficult to diagnose by echocardiography, suggesting an important diagnostic role for cardiac catheterization in these children.

Recommendations

1. **Minimizing peak inspiratory pressure and avoiding large tidal volumes are recommended to reduce ventilator-associated acute lung injury in infants with CDH (*Class I; Level of Evidence B*).**
2. **High-frequency oscillatory ventilation is a reasonable alternative mode of ventilation for subjects with CDH when poor lung compliance, low volumes, and poor gas exchange complicate the clinical course (*Class IIa; Level of Evidence B*).**
3. **iNO therapy can be used to improve oxygenation in infants with CDH and severe PH but should be used cautiously in subjects with suspected LV dysfunction (*Class IIa; Level of Evidence B*).**
4. **ECMO is recommended for CDH patients with severe PH who do not respond to medical therapy (*Class I; Level of Evidence B*).**
5. **Prostaglandin E_1 may be considered to maintain patency of the ductus arteriosus and to improve cardiac output for infants with CDH and suprasystemic levels of PH or RV failure to improve cardiac output (*Class IIb; Level of Evidence C*).**
6. **Evaluation for long-term PAH-specific therapy for PH in infants with CDH should follow recommendations for all children with PH, which includes cardiac catheterization (*Class I; Level of Evidence B*).**
7. **Longitudinal care in an interdisciplinary pediatric PH program is recommended for infants with CDH who have PH or are at risk of developing late PH (*Class I; Level of Evidence B*).**

7. Bronchopulmonary Dysplasia

BPD is the chronic lung disease of infancy that occurs in premature infants after oxygen and ventilator therapy for acute respiratory disease at birth. Despite striking changes in the nature and epidemiology of BPD over the past decades, PH continues to contribute significantly to high morbidity and mortality in BPD and can occur early in the course of disease.[259,260] Original descriptions of BPD reported striking pulmonary hypertensive vascular remodeling in severe cases and that the presence of PH beyond 3 months of age was associated with a high mortality rate (40%).[261] In the postsurfactant era, late PH continues to be strongly linked with poor survival in the "new BPD."[261–263] Severe PH beyond the first few months of life is associated with a 47% mortality within 2 years after diagnosis.[262]

Not only is PH a marker of more advanced BPD, but high PVR also causes poor RV function, impaired cardiac output, limited oxygen delivery, increased pulmonary edema, and possibly a higher risk for sudden death. PH in BPD is increasingly recognized in preterm infants with lower mortality risk, and retrospective studies have noted PH in roughly 25% to 37% of infants with BPD.[264–266] These retrospective studies are somewhat limited, however, by the selective assessment of PH by echocardiogram. The diagnosis of PH and other cardiovascular complications in infants with BPD can be difficult because clinical signs and symptoms of PH can be subtle or overlap with respiratory signs. On the basis of the strong correlations between PH and survival in BPD,[262] early detection of PH may provide helpful prognostic information and lead to the earlier application of more aggressive respiratory support, cardiac medications, vasodilators, and surgical or interventional cardiac catheterization procedures to improve late outcomes.

The lung circulation in BPD is characterized by abnormal (dysmorphic) growth, which includes reduced small pulmonary arteries and an altered pattern of distribution within the lung interstitium.[267] This reduction of alveolar-capillary surface area impairs gas exchange, which increases the need for prolonged oxygen and ventilator therapy, susceptibility for hypoxemia with acute respiratory infections and exercise, and the risk for developing severe PH. Experimental studies have further shown that early injury to the developing lung can impair angiogenesis, which contributes to decreased alveolarization.[268] Thus, abnormalities of the lung circulation in BPD not only are related to the presence or absence of PH but also are more broadly related to PVD resulting from decreased vascular growth, which also contributes to disease pathogenesis and abnormal cardiopulmonary physiology.

PAH in BPD includes increased vascular tone and vasoreactivity, hypertensive remodeling, and decreased vascular growth. Physiological abnormalities of the pulmonary circulation in BPD include elevated PVR and abnormal vasoreactivity, as evidenced by the marked vasoconstrictor response to acute hypoxia.[269,270] Cardiac catheterization studies have shown that even mild hypoxia can cause marked elevations in PAP in some infants with BPD, including infants with only modest basal elevations of PH.[270] Increased pulmonary vascular tone contributes to high PVR even in older children with BPD without hypoxia, suggesting that abnormal vascular

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function persists even late in the course.[271] Reduced vascular growth limits vascular surface area over time, causing further elevations of PVR, especially in response to high cardiac output with exercise or stress. Clinically, reduced vascular surface area implies that even relatively minor increases in left-to-right shunting of blood flow through a patent foramen ovale, ASD, or PDA may induce a far greater hemodynamic injury in infants with BPD than in infants with normal lung vascular growth.

In addition to PVD, LV diastolic dysfunction can contribute to high PAP in infants with BPD.[272] Up to 25% of infants with BPD with PH who were evaluated by cardiac catheterization had hemodynamic signs of LV diastolic dysfunction in a retrospective study.[271] Some infants with LV diastolic dysfunction present with persistent requirements for frequent diuretic therapy to treat recurrent pulmonary edema, even in the presence of only mild PH. Prominent bronchial and other systemic-to-pulmonary collateral vessels can be readily identified in many infants during cardiac catheterization. Although collateral vessels are generally small, large collaterals may contribute to significant shunting of blood flow to the lung, causing edema and the need for higher Fio_2. Finally, pulmonary vein stenosis is strongly associated with PH in infants with BPD and may contribute to progressive PVD and recurrent pulmonary edema.[273]

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7.1. Diagnostic Approach

We recommend early echocardiograms for the diagnosis of PH in preterm infants with severe respiratory distress syndrome who require high levels of ventilator support and supplemental oxygen, especially in the setting of oligohydramnios and intrauterine growth restriction.[274] Infants with more severe prematurity (<26 weeks) are at highest risk for late PH.[275] Similarly, infants with a particularly slow rate of clinical improvement, as manifested by persistent or progressively increased need for high levels of respiratory support, should be assessed for PH. In the setting of established BPD, preterm infants who at a corrected age of 36 weeks still require positive-pressure ventilation support, are not weaning consistently from oxygen, have oxygen needs at levels disproportionate to their degree of lung disease, or have recurrent cyanotic episodes warrant screening for PH or related cardiovascular sequelae. Other clinical markers often associated with more severe disease include feeding dysfunction and poor growth, recurrent hospitalizations, and elevated $Paco_2$. High $Paco_2$ is a marker of disease severity and reflects significant airways obstruction, abnormal lung compliance with heterogeneous parenchymal disease, or reduced surface area and is an indication for PH screening.[276] Another strategy would be to use echocardiograms to screen every patient at 36 weeks of age who is diagnosed with moderate or severe BPD, but how often PH would be missed in patients with milder BPD is uncertain.

Serial electrocardiograms may have inadequate sensitivity and positive predictive value for identification of RVH as a marker of PH. Some patients can have significant RVH and PH despite minimal or normal ECG findings. As a result, we recommend echocardiograms to screen for PH in patients with BPD, with serial studies performed at 4- to 6-month intervals, depending on changes in clinical course, as reflected by such markers as recurrent respiratory exacerbations, lack of improvement in oxygen requirement, severity of PH, and changes in drug therapy. Estimated systolic PAP derived from the TR jet velocity as measured by echocardiogram has become one of the most used findings for evaluating PH. Past studies have shown excellent correlation coefficients (r values between 0.93 and 0.97) compared with cardiac catheterization measurements in children <2 years of age with CHD.[15,277] However, the utility of echocardiogram to define the presence or severity of PH in BPD may be less favorable.[29] In this study, systolic PAP could be estimated in only 61% of studies, and there was poor correlation between echocardiogram and subsequent cardiac catheterization measures of systolic PAP in these infants. Echocardiogram estimates of systolic PAP correctly identified the presence or absence of PH in 79% of these studies, but the severity of PH was correctly assessed in only 47% of those studies. Seven of 12 children (58%) without PH by echocardiogram had PH during subsequent cardiac catheterization. In the absence of a measurable TR jet, qualitative echocardiogram findings of PH, including RA enlargement, RV hypertrophy, RV dilation, pulmonary artery dilation, and septal flattening, either alone or in combination, have relatively poor predictive value. Factors associated with chronic lung disease, specifically marked pulmonary hyperinflation, expansion of the thoracic cage, and alteration of the position of the heart, adversely affect the ability to detect and measure TR jet velocities.[278] Thus, as used in clinical practice, echocardiography often identifies PH in infants with BPD, but estimates of systolic PAP were not obtained consistently and were often not reliable for determining disease severity. Despite its limitations, echocardiography remains the best available screening tool for PH in BPD patients.

In patients with PH by echocardiogram, we generally recommend cardiac catheterization for patients with BPD (1) who have persistent signs of severe cardiorespiratory disease or clinical deterioration not directly related to airways disease; (2) who are suspected of having significant PH despite optimal management of their lung disease and associated morbidities; (3) who are candidates for long-term PH drug therapy; and (4) who have unexplained, recurrent pulmonary edema. The goals of cardiac catheterization are to assess the severity of PH; to exclude or document the severity of associated anatomic cardiac lesions; to define the presence of systemic-pulmonary collateral vessels, pulmonary venous obstruction, or LV diastolic dysfunction; and to assess pulmonary vascular reactivity in patients who fail to respond to oxygen therapy alone. Other critical information can be acquired during cardiac catheterization that may significantly aid in the management of infants with BPD. In particular, assessment of the physiological role of shunt lesions, especially ASD or PFO; assessment of the presence, size, and significance of bronchial or systemic collateral arteries; determination of the presence of pulmonary artery stenosis; and structural assessments of the pulmonary arterial and venous circulation by angiography are among several key factors that may affect cardiopulmonary function. A recent report highlighted the importance of pulmonary vein stenosis in premature infants, but its prevalence is currently unknown.[273] Importantly, elevated pulmonary capillary wedge or LA pressure may signify LV systolic or diastolic

dysfunction. LV diastolic dysfunction can contribute to PH, recurrent pulmonary edema, or poor iNO responsiveness in infants with BPD, and measuring changes in pulmonary capillary wedge pressure and LA pressure during AVT may help with this assessment.

7.2. Treatment

Management of PH in infants with BPD begins with aggressively treating the underlying lung disease. This includes an extensive evaluation for chronic reflux and aspiration, evaluation for structural airway abnormalities (such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, tracheomalacia and other lesions), assessment of bronchoreactivity, improvement of lung edema and airway function, and others. Periods of acute hypoxia, whether intermittent or prolonged, are common causes of persistent PH in BPD.[279] Brief assessments of oxygenation (spot checks) are not sufficient for decisions on the level of supplemental oxygen needed. Targeting oxygen saturations to 92% to 94% is sufficient to prevent the adverse effects of hypoxia in most infants without increasing the risk of additional lung inflammation and injury. A sleep study may be necessary to determine the presence of noteworthy episodes of hypoxia and whether hypoxemia has predominantly obstructive, central, or mixed causes.

Additional studies that may be required include flexible bronchoscopy for the diagnosis of anatomic and dynamic airway lesions (such as tracheomalacia) that may contribute to hypoxemia and poor clinical responses to oxygen therapy. Upper gastrointestinal series, pH or impedance probe, and swallow studies may be indicated to evaluate for gastroesophageal reflux and aspiration that can contribute to ongoing lung injury. For patients with BPD and severe PH who fail to maintain near-normal ventilation or require high levels of Fio_2 despite conservative treatment, consideration should be given to long-term mechanical ventilatory support. Despite the growing use of pulmonary vasodilator therapy for the treatment of PH in BPD, data demonstrating efficacy are extremely limited, and the use of these agents should only follow thorough diagnostic evaluations and aggressive management of the underlying lung disease.

Current therapies used for PH therapy in infants with BPD generally include iNO, sildenafil, ERAs, and CCBs.

iNO causes selective pulmonary vasodilation[271] and improves oxygenation in infants with established BPD.[280] Although long-term iNO therapy has been used in infants with BPD, efficacy data are not available. iNO therapy is often initiated at doses of 10 to 20 ppm; however, most patients subsequently tolerate weaning of to 2 to 10 ppm. The lower dose may further enhance ventilation-perfusion matching, allowing better oxygenation at lower FiO_2.

In a study of 25 infants with chronic lung disease and PH (18 with BPD), prolonged sildenafil (0.5–2 mg/kg 3 times daily) therapy as part of an aggressive program to treat PH was associated with an improvement in PH by echocardiogram in 88% of patients without significant rates of adverse events.[257] Although the time to improvement was variable, many patients were able to wean off mechanical ventilator support and other PH therapies, especially iNO, during the course of sildenafil treatment without worsening of PH.

Short-term benefits of CCBs have been reported in infants with BPD.[279,281,282] Nifedipine can acutely lower PAP and PVR in children with BPD, but the effects of nifedipine on PAP were not different from the effects of supplemental oxygen alone. Compared with a short-term study of iNO reactivity in BPD, the acute response to CCB was poor, and some infants developed systemic hypotension. Intravenous PGI_2 analogs (epoprostenol, treprostinil) have been used in some infants with BPD and late PH,[283] but concerns about its potential to worsen gas exchange, by increasing ventilation-perfusion mismatch and to cause systemic hypotension have limited its use in BPD. Although another stable PGI_2 analog, iloprost, is available for inhalational use, the need for frequent treatments (6–8 times daily) and occasional bronchospasm may limit its use in BPD.[284]

In addition to close monitoring of pulmonary status, infants with BPD and PH should be followed up by serial echocardiograms, which should be obtained at least every 2 to 4 weeks with the initiation of therapy and at 4- to 6-month intervals with stable disease. Abrupt worsening of PH may reflect several factors, including the lack of patient compliance with oxygen therapy or medication use. However, worsening of PH may be related to the progressive development of pulmonary vein stenosis. Repeat cardiac catheterization may be indicated for patients being treated for PH with vasodilator therapy who experience clinical deterioration or worsening PH by echocardiogram or who have nondiagnostic echocardiograms. We recommend weaning medications when serial echocardiograms are normal or nearly normal. Biomarkers such as BNP and NT-proBNP levels may be useful for long-term follow-up, but whether the use of these biomarkers improves outcomes is unknown.

Recommendations

1. **Screening for PH by echocardiogram is recommended in infants with established BPD (*Class I; Level of Evidence B*).**
2. **Evaluation and treatment of lung disease, including assessments for hypoxemia, aspiration, structural airway disease, and the need for changes in respiratory support, are recommended in infants with BPD and PH before initiation of PAH-targeted therapy (*Class I; Level of Evidence B*).**
3. **Evaluation for long-term therapy for PH in infants with BPD should follow recommendations for all children with PH and include cardiac catheterization to diagnose disease severity and potential contributing factors such as LV diastolic dysfunction, anatomic shunts, pulmonary vein stenosis, and systemic collaterals (*Class I; Level of Evidence B*).**
4. **Supplemental oxygen therapy is reasonable to avoid episodic or sustained hypoxemia and with the goal of maintaining O_2 saturations between 92% and 95% in patients with established BPD and PH (*Class IIa; Level of Evidence C*).**
5. **PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying**

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respiratory and cardiac disease (*Class IIa; Level of Evidence C*).

6. **Treatment with iNO can be effective for infants with established BPD and symptomatic PH (*Class IIa; Level of Evidence C*).**
7. **Serial echocardiograms are recommended to monitor the response to PAH-targeted therapy in infants with BPD and PH (*Class I; Level of Evidence B*).**

8. Pharmacotherapy

On the basis of known mechanisms of action, 3 classes of drugs have been extensively evaluated for the treatment of pediatric PAH: prostanoids (epoprostenol, treprostinil, iloprost, beraprost), ERAs (bosentan, ambrisentan), and PDE5 inhibitors (sildenafil, tadalafil; Table 3). Because vasoconstriction is considered an important component in the development of PAH, vasodilator drugs are frequently used to decrease PAP, to improve cardiac output, and to potentially reverse pulmonary vascular changes in the lung. However, emerging evidence suggests an important role for cellular growth, inflammation, and fibroproliferative changes in PAH that may not be adequately addressed by current therapies, perhaps explaining continuing disease morbidity and mortality. Therapy in adults is evidence based, consistently derived from ≥1 clinical trials,[285–290] whereas therapy in children is generally based on experience and small observational studies. The long-term strategy for the treatment of PH in children (Figures 2 and 3) has been extrapolated from the adult evidence-based recommendations,[291,292] although it is difficult to place very young children in the WHO classification owing to the lack of exercise standards in children <8 years of age and a limited body of RCT data to guide therapy.[292] Expert consensus suggests that targeted PAH therapy has improved survival in IPAH and HPAH, although the effects of PAH-targeted therapy in repaired and unrepaired PAH associated with CHD are less clear.[105]

Before targeted PAH therapy for chronic PAH is started, vasodilator responsiveness should be assessed by cardiac catheterization, and anatomic obstruction resulting from pulmonary venous disease or left-sided heart disease should be excluded (Figure 3). A positive response to AVT is defined by assessing the change in hemodynamic parameters to vasodilators, as previously described. With IPAH/HPAH, the younger the child is at the time of testing, the greater the likelihood of positive AVT responsiveness is.[111,293,294] A recent comparison of different vasodilator response criteria to determine suitability for CCB therapy showed that acute vasodilator testing was always more likely in IPAH/HPAH compared with PAH-CHD. Furthermore, no responders were identified in patients with a posttricuspid shunt. An acute vasodilator response has also been associated with improved survival in children.[295,296]

8.1. Conventional Therapy

Conventional therapies typically used for heart failure are also used for the treatment of the patient with RV failure. Diuretic therapy should be initiated cautiously because patients with PAH are often preload dependent to maintain an optimal cardiac output. Digitalis may be beneficial in patients with overt right-sided cardiac dysfunction and clinical failure, but data are lacking.[297] The benefit of long-term anticoagulation has not been studied in children with PAH, but its use is recommended in patients with IPAH/HPAH, patients in low cardiac output, those with hypercoagulable states, and those with a long-term indwelling intravenous catheter. Even in adults with group 1 PAH, the benefits of warfarin are largely inferred from retrospective analyses in IPAH/HAPH and anorexigen-induced PAH patients, and there are no RCTs. However, retrospective data in adults dying of IPAH/HPAH provide biological plausibility because 57% had thromboemboli.[298]

Subsequent noncontrolled, prospective and retrospective studies showed that treatment of PAH patients improved survival, leading to the general recommendation that adults with IPAH/HPAH be treated with anticoagulation, although evidence for treating adult patients with PAH associated with CHD with anticoagulants is less clear.[298–300] Furthermore, the use of other anticoagulant drugs such as aspirin has not been well studied. The risk-to-benefit ratio for anticoagulation should be wisely weighed, especially in small children prone to hemorrhagic complications, and anticoagulation should not be used in those with HHT or PPHTN. In IPAH and HPAH, the aim is to maintain an international normalized ratio between 1.5 and 2.0, although this is an empirical therapeutic target. The use of anticoagulation in patients with Eisenmenger syndrome (ES) is controversial, and the potential risks and benefits of anticoagulation in this setting must be carefully considered because there is a significant risk of pulmonary hemorrhage.[301]

Children with PH are at risk for worse complications of routine childhood illnesses and should have routine vaccinations as generally recommended. Respiratory syncytial virus, pertussis, and influenza may exacerbate PH and may cause greater morbidity in children with PH.

8.2. Calcium Channel Blockers

The use of CCBs to evaluate vasoreactivity has significant potential risks because these drugs can cause a decrease in cardiac output or a marked drop in systemic blood pressure.[302] Consequently, elevated RA pressure and low cardiac output are contraindications to short- or long-term CCB. An acute trial of CCB therapy should be performed only in those patients who have previously been shown to be acutely reactive to either iNO or intravenous epoprostenol. Likewise, patients who do not have an acute vasodilator response to short-acting agents and who are then placed on CCB are unlikely to benefit long term and, more important, are at risk of a fatal outcome.[302]

An adaptation of the conventional pediatric definition of a response to AVT for determination of suitability for CCB therapy is a 20% decrease in mPAP, an increase or lack of a decrease in cardiac output, and no change or a decrease in the PVR/SVR ratio.[302] Note that this is not the definition used for adult PAH, nor is this definition used to assess operability in PAH associated with CHD. The current definition for an acute response in an adult PAH patient is defined as a decrease in mPAP >10 to <40 mm Hg with no change or an increase in cardiac output; this definition appears to predict long-term response to CCB therapy in adult IPAH/HPAH.[103] In REVEAL, when the adaptation of the conventional pediatric definition was used, 36 of 102 children (35%) with IPAH/

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AHA/ATS Consensus Pediatric PAH: Disease Severity

LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
I,II	WHO class	III,IV
None	Syncope	Recurrent syncope
Minimal RV enlargement/dysfunction	Echocardiography	Significant RV enlargement/dysfunction Pericardial effusion
PVRI <10 WU•m^2 CI >3.0 L/min/m^2 PVR/SVR <0.5	Hemodynamics	PVRI >20 WU•m^2 CI <2.0 L/min/m^2 PVR/SVR >1.0
Minimally elevated	BNP / NTproBNP	Significantly elevated
Longer (>500 m)	6MWD	Shorter (<300 m)
Peak VO_2 >25 mL/kg/min	CPET	Peak VO_2 <15 mL/kg/min

Figure 2. Features that distinguish severity of disease in pediatric pulmonary arterial hypertension. AHA indicates American Heart Association; ATS, American Thoracic Society; BNP, brain natriuretic peptide; CI, cardiac index; CPET, cardiopulmonary exercise testing; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; RV, right ventricular; 6MWD, 6-minute walk distance; SVR, systemic vascular resistance; WHO, World Health Organization; and WU, Wood units. Modified from McLaughlin et al.[302a] Copyright © 2006, American Heart Association.

HPAH were acute responders compared with 9 of 60 patients (15%) with PAH associated with CHD (P=0.006); thus, patients with repaired CHD are less likely to be responsive to AVT than those with IPAH.[1,295]

For acute responders with IPAH treated with CCB, survival was 97%, 97%, and 81% at 1, 5, and 10 years, respectively, and sustained treatment success was 84%, 68%, and 47%, respectively.[296] However, inappropriate use of CCB therapy results in a very poor outcome. IPAH children who were not reactive during AVT but were still treated with CCB had survival rates of 45%, 34%, 29%, and 29% at 1, 2, 3, and 4 years. CCBs are contraindicated in children who have not undergone AVT, are nonresponders, or have RV failure (ie, WHO functional class IV), regardless of acute response. The last prohibition reflects the potential negative inotropic effect of CCBs, especially in patients with low cardiac output.[302] Because the negative inotropic effects of CCBs are more prominent in children <1 year of age, CCBs are usually not recommended at this age. Unfortunately, the majority of children with severe PAH are nonresponsive to AVT, and therapy other than a CCB is usually required.

Long-term CCB therapies recommended for use in acute responders include nifedipine (2–5 mg·kg^{-1}·d^{-1}), diltiazem (3–5 mg·kg^{-1}·d^{-1}), and amlodipine (2.5–10 mg/d). These agents, particularly diltiazem, may lower heart rate, and diltiazem is used more frequently in young children with higher heart rates. Verapamil is contraindicated in PAH because of its negative inotropic effects, minimal pulmonary vasoreactive properties, and tendency to cause bradycardia.

8.3. PGI_2 Analogs

Adults with IPAH or HPAH and children with CHD have an imbalance in the biosynthesis of thromboxane A_2 and PGI_2, favoring thromboxane A_2 and vasoconstriction.[303] Likewise, adults and children with severe PAH show diminished PGI_2 synthase expression in the lung vasculature.[304] PGI_2 and PGI_2 analogs stimulate the cAMP pathway to increase pulmonary vasodilation. Intravenous PGI_2 was first used in PPHN[305] in 1979 and continues to be the gold standard for treatment of severe PAH with RV failure. Epoprostenol, the first PGI_2 analog, was approved for adults by the US FDA in 1995. Long-term use of intravenous epoprostenol improves survival and quality of life in adults and children with IPAH.[302,304–308] Improved survival has been shown in children who were treated with long-term intravenous epoprostenol, with a 4-year survival rate of 94% for treated children[302] and a 10-year treatment success

AHA/ATS Consensus Pediatric PAH Treatment Algorithm

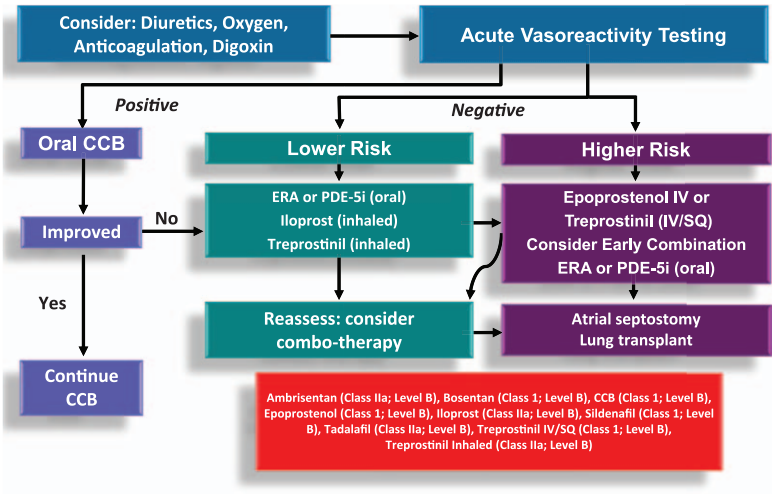

Figure 3. Algorithm illustrating the pharmacological approach to pediatric pulmonary arterial hypertension (PAH). AHA indicates American Heart Association; ATS, American Thoracic Society; CCB, calcium channel blocker; ERA, endothelin receptor antagonist; and PDE-5i, phosphodiesterase type 5 inhibitor. Modified from Ivy et al[308a] with permission from the publisher. Copyright © 2013, Elsevier.

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rate (freedom from death, transplantation, or AS) of 37%.[296] A study from the United Kingdom reported IPAH survival rates of 86%, 80%, and 72% at 1, 3, and 5 years, respectively, compared with a survival time of <1 year in historical untreated controls, but this is in adults.[309] A combination of intravenous epoprostenol with oral bosentan, oral sildenafil, or both may result in a better survival, but this was reported only in an observational cohort, not a randomized trial.[104,105]

Patients with severe PAH and CHD may also respond favorably to intravenous epoprostenol.[310] The starting dose for epoprostenol is usually 2 $ng \cdot kg^{-1} \cdot min^{-1}$, which is steadily increased until side effects such as nausea, diarrhea, jaw pain, bone pain, and headaches develop. The effective dose of epoprostenol in children is frequently higher than in adults, with a broad range of optimal dosing from 40 to >150 $ng \cdot kg^{-1} \cdot min^{-1}$ and an average dose of ≈80 $ng \cdot kg^{-1} \cdot min^{-1}$. Uptitration of epoprostenol over time may be needed to maintain optimum effect, but excessive doses of epoprostenol may result in a high-output state requiring downtitration.[311] The treatment of patients with PGI_2 is challenging. Intravenous epoprostenol must be infused 24 hours a day via a central venous catheter and kept cold with ice packs; the half-life of the drug is 2 to 5 minutes, placing the patient at risk for an acute rebound PHC if there is an accidental discontinuation of the medication. Complications such as sepsis, local site infection, and catheter dislodgement are common and can be responsible for life-threatening sepsis or rebound PH.[312,313] Recently, the use of specific closed-hub systems has been described in children to decrease the risk of catheter-related infection.[314]

Some children have an exceptional clinical response to intravenous epoprostenol, which includes near normalization of PAP. This subset of children may eventually be transitioned from intravenous to oral therapy with close monitoring.[315,316] However, this should be considered only in a pediatric PH center with significant experience in treating children with PAH owing to the potential for significant adverse response in some children who may not be candidates for weaning from intravenous epoprostenol to oral/inhaled dugs. Inhaled epoprostenol has been used in the critical care setting.[317] A generic form of epoprostenol and a form that is stable at room temperature are FDA approved in adults.

The PGI_2 analog treprostinil was approved by the FDA in 2002 for subcutaneous use, in 2004 for intravenous administration, and in 2009 for inhaled administration and 2013 for oral administration in adults. In contrast to epoprostenol, treprostinil is chemically stable at room temperature with a neutral pH and has a longer half-life (elimination half-life, 4.5 hours; distribution half-life, 40 minutes), thereby permitting continuous subcutaneous infusion.[318] Subcutaneous treprostinil allows patients to remain free of central venous catheters, and recent data have shown long-term efficacy in adults with PAH.[319] In its subcutaneous form, discomfort at the infusion site is common and represents a limitation of this route of administration. However, a recent study of subcutaneous treprostinil in young children showed promise with tolerable side effects.[320] Anticipatory treatment of site pain, including the initial use of a "dry-site" histamine blocker and low-dose narcotic therapy, for the first several days after site initiation may be beneficial. Treprostinil in the intravenous form requires central venous access and continuous infusion, but it is stable at room temperature, is easier for families to mix, has a half-life of 2 to 4 hours, and requires smaller pumps. An increase in catheter-related and Gram-negative bloodstream infections among patients with PAH treated with intravenous treprostinil has been noted, but this risk may be mitigated by using watertight seals throughout the delivery system, using closed-hub systems, and changing the diluent of treprostinil to epoprostenol diluent.[313,314,321,322] Intravenous treprostinil may have fewer side effects than intravenous epoprostenol, but no studies have directly compared both agents.[323] Treprostinil has also been given in an inhaled form,[324] and studies have recently been published in children.[325]

Another PGI_2 analog, iloprost, has been approved as an inhalational agent for the treatment of adult PAH in the United States in 2004. Iloprost is administered by nebulization 6 to 9 times a day and requires patient cooperation, with treatment administration lasting 10 to 15 minutes, which is difficult for young children.[294,326,327] The advantage of an inhaled PGI_2 is that it can cause pulmonary vasodilation with minimal effect on systemic blood pressure.[327,328] An increase in airway reactivity has been noted in some children receiving inhaled iloprost.[284] Inhaled iloprost has also been studied in combination with bosentan and sildenafil, among others, but definitive studies of efficacy in children are lacking.[329–331]

Beraprost is an orally active PGI_2 analog with a half-life of 35 to 40 minutes. Although beneficial effects have been noted in short-term trials, the effects appeared to be attenuated with prolonged treatment.[332,333] Data in children are scarce, and beraprost is not available in the United States or Europe.[334] Long-acting berapost is also approved for adult PAH in South Korea and Japan.[335]

8.4. ET Receptor Antagonists

The effects of ET-1 are mediated through 2 receptor subtypes, ET_A and ET_B. ET_A and ET_B receptors on vascular smooth muscle mediate vasoconstriction, whereas ET_B receptors on endothelial cells cause release of NO and PGI_2 and act as clearance receptors for circulating ET-1. ET_A receptors have recently been described on pulmonary artery endothelial cells.[336] ET-1 expression is increased in the pulmonary arteries of patients with PH.[337–339] Side effects of ET antagonists include elevation of hepatic aminotransferase levels, teratogenicity, anemia, peripheral edema (which may relate to negative inotropic effects on the RV), decreased effectiveness of oral contraceptive agents, and effects on male fertility. Long-term monitoring of liver function tests with bosentan is mandated. However, ambrisentan treatment no longer requires monthly liver function test monitoring owing to the rarity of elevations of hepatic aminotransferase levels. Nonetheless, many clinicians continue monitoring patients on ambrisentan.

Bosentan, a dual ERA, lowers PAP and PVR and improves exercise capacity in adults with PAH,[286] and similar results have been reported in children.[315,340–346] Bosentan lowers PAP and PVR and is well tolerated in children with IPAH or PAH associated with CHD.[343,344,347] Elevated hepatic aminotransferase levels occur in ≈11% of adults and 3% of children treated with bosentan. In a 12-week study, bosentan was well tolerated and lowered the PAP and PVR children with IPAH or

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PAH related to CHD.[343] A retrospective study of 86 children on bosentan for a median exposure of 14 months, with and without concomitant therapy, reported that bosentan caused sustained clinical and hemodynamic improvement and was well tolerated, with 2-year survival estimates of 91%.[342] Follow-up of these patients at 4 years revealed that the Kaplan-Meier estimate of disease progression in patients on bosentan was high (54%), with a survival estimate of 82%.[348] Bosentan therapy provided short-term improvement in WHO functional class and 6MWD test in children and adults with PAH and systemic-to-pulmonary shunt.[349] This beneficial response progressively declined after 1 year, with a more rapid decline observed in children, who tended to have more severe disease at baseline than adults.[349]

The safety of bosentan therapy in children with PAH has recently been reviewed.[350] Elevated transaminase levels were reported in 2.7% of children compared with 7.8% of patients ≥12 years of age, and the overall discontinuation rate from bosentan was 14% in children compared with 28% in patients ≥12 years of age. Importantly, bosentan pharmacokinetics were not altered by concurrent sildenafil therapy.[346] Bosentan has been studied in adult patients with ES in a placebo-controlled trial, showing few adverse events and improved exercise capacity and hemodynamics.[288] Other studies have further demonstrated beneficial effects of bosentan in patients with ES.[351,352] A specific water-soluble, cloverleaf formulation has been recently approved for use in children with PAH in Europe.[353]

Selective ET_A receptor blockade with ambrisentan may benefit patients with PAH by blocking the vasoconstrictor effects of ET_A receptors while maintaining the vasodilator and clearance functions of ET_B receptors. Ambrisentan was approved by the FDA in June 2007 for adults with WHO group 1 PAH. Adults had improvements in 6MWD and delays in clinical worsening on ambrisentan.[354] The incidence of elevated liver function tests was 2.8%, which was similar to that of the placebo group.[290] Short-term use of ambrisentan improved 6MWD in 17 patients with ES.[355] In a retrospective study, 38 pediatric PAH patients were treated with ambrisentan as add-on therapy or as replacement therapy for bosentan.[356] In both groups, mPAP and functional class improved during the follow-up, but 1 patient required an AS because of disease progression.[356] Macitentan has been approved in adults with PAH with no studies currently reported in children.

8.5. PDE Inhibitors

PDE5 expression and activity are increased in PH,[357,358] and specific PDE5 inhibitors such as sildenafil or tadalafil increase smooth muscle cell cGMP levels and promote pulmonary vascular dilation and remodeling.[287,359–363] Sildenafil was approved by the FDA for group 1 PAH in 2005; its intravenous formulation was approved in 2009.[387] Early evaluation of sildenafil in 14 children with PAH showed an increase in 6MWD from 278±114 to 443±107 m over 6 months (P=0.02); at 12 months, the distance walked was 432±156 m (P=0.005) and was associated with a decrease in mPAP and PVR.[364] In several small studies of children with PPHN, IPAH, and PH associated with CHD, sildenafil has been shown to improve exercise capacity and hemodynamics.[105,113,215,257,258,362,363,365–368] Sildenafil may also be useful in the setting of iNO therapy withdrawal,[367,369–371] in postoperative PH,[368,372] or in the presence of PH related to chronic lung disease.[330]

In a 16-week randomized, double-blind, placebo-controlled study of treatment naive children (Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension [STARTS-1]), the effects of oral sildenafil in pediatric PAH were studied.[292] Children (n=235) with IPAH or PAH associated with CHD (age, 1–17 years.; weight ≥8 kg) received low-, medium-, or high-dose sildenafil or placebo 3 times daily. The primary end point was percent change in peak oxygen consumption from baseline to week 16 for combined treatment groups. Exercise testing was performed only in children able to exercise reliably. Secondary end points, including mPAP, PVR, and functional class, were assessed in all enrolled patients, including those unable to exercise reliably. The percentage change in peak oxygen consumption for the treatment group versus the placebo group was 7.7±4.0% (95% confidence interval, –0.2 to 15.6; P=0.056). Peak oxygen consumption, functional capacity, mPAP, and PVR improved with the medium- and high-dose groups compared with placebo, whereas the low dose was ineffective.

The dose-extension study (STARTS-2) was blinded until all patients completed STARTS-1. After study patients completed 3 years of treatment, an increased risk of mortality was found in patients who were originally randomized to high dose at the beginning of the 16-week study or former placebo patients who were later randomized to the high dose at the beginning of the extension study. After 3 years, the incidence of mortality was 9% (5 of 55), 14% (10 of 74), and 20% (20 of 100) in the groups receiving low-, medium-, and high-dose sildenafil, respectively. Overall, the risk for mortality was greatest in older patients with IPAH who had higher mPAP and PVRI at enrollment. Children weighing <20 kg and those with PAH associated with CHD did not have the same mortality risk as other subgroups in the study. Although the causality of this observed increased mortality at 3 years is not known, high-dose sildenafil carries an unfavorable risk-to-benefit ratio when used as monotherapy.[292]

After review of these data, sildenafil was approved by the European Medicines Agency for the treatment of children with PAH who are 1 to 17 years of age. The European Medicines Agency cited efficacy in terms of improvement in exercise capacity or pulmonary hemodynamics in IPAH and PH associated with CHD. Because of concerns of increased mortality at higher doses, the European Medicines Agency recommended a dose of 20 mg 3 times a day for children >20 kg and 10 mg 3 times a day for children <20 kg. In contrast, the US FDA recommended that sildenafil not be prescribed to children (between 1 and 17 years of age) for PAH. The FDA decision against the use of sildenafil was based also on data from the STARTS-1 and STARTS-2 studies but emphasized that children taking a high dose of sildenafil had a higher risk of death than those taking a low dose, whereas the low doses of sildenafil did not improve exercise ability. Current recommendations include following European Medicines Agency guidelines for treatment with low doses and close follow-up to determine the need for changes in therapy as indicated.[373]

A recent study showed that intravenous sildenafil improves oxygenation index in PPHN in patients treated with or without

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iNO.[215] However, sildenafil infusion can increase intrapulmonary shunting and worsen hypoxemia in the postoperative CHD patient.[114,374] Tadalafil, a long-acting PDE5 inhibitor, received FDA approval in 2009 in adults with group 1 PAH. A placebo-controlled study demonstrated that tadalafil improved exercise capacity, time to clinical worsening, and health-related quality of life in adult patients with IPAH or associated PAH.[289]

Open-label use of tadalafil has suggested benefit in ES and in combination with PGI_2.[289,375–378] A recent retrospective study demonstrated the safety and potential efficacy of tadalafil therapy in 33 pediatric patients with PAH.[379] In this study, 29 of 33 patients were switched from sildenafil to tadalafil. The average doses of sildenafil and tadalafil were 3.4±1.1 and 1.0±0.4 $mg \cdot kg^{-1} \cdot d^{-1}$, respectively. In 14 of 29 children transitioned from sildenafil to tadalafil, repeat cardiac catheterization showed significant improvements in mPAP and PVRI. Vardenafil, another selective PDE5 inhibitor, was recently studied in a placebo-controlled RCT in adults in China and improved 6MWD; however, it is not FDA approved.[380]

8.5.1. Combination Therapy

Combination therapy is an attractive option to simultaneously address multiple pathways involved in the pathophysiology of PAH that potentially provide synergistic benefits that allow sustained improvement compared with monotherapy. However, few studies have been performed that specifically examined combination therapies, and the high cost of this strategy is an important consideration. A therapeutic approach using the combination of bosentan, sildenafil, and inhaled iloprost may improve survival and reduce the need for lung transplantation in adult patients with severe PAH.[381] Whether combination therapy should be used as a first step through concurrent initiation of ≥2 drugs or as add-on therapy is still not known, and more studies are clearly needed.

Recommendations

1. **Supportive care with digitalis and diuretic therapy is reasonable with signs of failure of the right side of the heart but should be initiated cautiously (*Class IIb; Level of Evidence C*).**
2. **Recommendations for long-term anticoagulation with warfarin include the following:**
   a. **Anticoagulation with warfarin may be considered in patients with IPAH/HPAH, patients with low cardiac output, those with long-term indwelling catheters, and those with hypercoagulable states (*Class IIb; Level of Evidence C*).**
   b. **Targeting the therapeutic range for international normalized ratio between 1.5 and 2.0 is recommended for young children with PAH (*Class I; Level of Evidence C*).**
   c. **Anticoagulation should not be used in young children with PAH because of concerns for harm from hemorrhagic complications (*Class III; Level of Evidence C*).**
3. **Oxygen therapy is reasonable for hypoxemic PAH patients who have oxygen saturations <92%, especially with associated respiratory disease (*Class IIa; Level of Evidence B*).**
4. **Recommendations for a trial of CCBs include the following:**
   a. **CCBs should be given only to those patients who are reactive as assessed by AVT and are >1 year of age (*Class I; Level of Evidence C*).**
   b. **CCBs are contraindicated in children who have not undergone or are nonresponsive to AVT and in patients with right-sided heart dysfunction because of the potential for negative inotropic effects of CCB therapy (*Class III; Level of Evidence C*).**
5. **Oral PAH-targeted therapy in children with lower-risk PAH is recommended and should include either a PDE5 inhibitor or an ERA (*Class I; Level of Evidence B*).**
6. **A goal-targeted therapy approach in which PAH-specific drugs are added progressively to achieve specified therapeutic targets can be useful (*Class IIa; Level of Evidence C*).**
7. **Intravenous and subcutaneous PGI_2 or its analogs should be initiated without delay for patients with higher-risk PAH (*Class I; Level of Evidence B*).**
8. **Recommendations for transition from parenteral to oral or inhaled therapy include the following:**
   a. **May be considered in asymptomatic children with PAH who have demonstrated sustained, near-normal pulmonary hemodynamics (*Class IIb; Level of Evidence C*).**
   b. **Requires close monitoring in an experienced pediatric PH center (*Class I; Level of Evidence B*).**

9. Isolated PAH

Isolated PAH includes IPAH and HPAH, which are rare but lethal conditions in children and adults, with an estimated incidence and prevalence of 0.7 and 4.4 per million children, respectively.[382] These diseases are included in the group 1 WHO classification of PAH.[5] Isolated PAH is characterized by progressive obliteration of the pulmonary vascular bed, leading to right-sided heart failure and death if left untreated. Patients are classified as idiopathic when no other associated condition can be identified; thus, IPAH is a diagnosis of exclusion. Fortunately, in the past 2 decades, there have been dramatic improvements in diagnostic techniques to facilitate the assessment of isolated PAH and novel drug developments, which have afforded children with isolated PAH improvements in their clinical course.[1,104,106]

PAH resulting from PVOD and pulmonary capillary hemangiomatosis is also included in this classification. PVOD is a rare disorder that is often initially misdiagnosed as IPAH. The annual incidence of PVOD based on the French National Registry is 0.1 to 0.2 cases per 1 million in the general population. This is likely an underestimation because patients are often not definitively diagnosed.[162] The diagnosis can be made across the entire age spectrum as early as the neonatal period. When the patient fails to respond or worsens in response to targeted PAH therapies, the diagnosis is often uncovered. PVOD accounts for ≈5% to 10% of cases initially diagnosed as idiopathic as a result of the similar clinical presentation.[383] The only definitive way to make this diagnosis is by lung biopsy, which is not without risk for this patient population. However,

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a lung biopsy should be performed with a high suspicion of PVOD in addition to a high-resolution noncontrast CT scan of the chest and pulmonary function tests. The histopathologic hallmark of PVOD is widespread fibrous intimal proliferation that involves predominantly pulmonary venules and small veins, whereas IPAH is characterized by frequent plexiform and possible thrombotic lesions.[384,385] Histological proof is generally required to make the diagnosis of PVOD, although the development of rapid onset or "flash" pulmonary edema during vasodilator treatment and the absence of elevated PA occlusion pressure and LA pressure are typically noted. The only long-term treatment for PVOD is lung transplantation, and early referral to an experienced transplantation center is critical for long-term survival.

Pulmonary capillary hemangiomatosis is a rare disease that is characterized by abnormal angiogenesis confined to the lung. Histopathological findings of pulmonary capillary hemangiomatosis (which has been renamed pulmonary microvasculopathy) include proliferation of capillary-sized vessels within the alveolar walls, interstitium, and postcapillary venules of the lung. Intimal thickening and medial hypertrophy of the small muscular pulmonary arteries are present, which are similar to the findings for other types of PAH, resulting in elevated PVR. The pathogenesis of pulmonary capillary hemangiomatosis is unknown, and there are no effective medical therapies. Lung transplantation is curative; however, because of the lack of awareness and the difficulty in making this diagnosis, the majority of reported cases have been discovered postmortem.[386] If pulmonary capillary hemangiomatosis is suspected by radiographic imaging or failure to respond to targeted PAH therapy, one should consider performing a lung biopsy because the only definitive treatment is lung transplantation.[387,388] Novel treatments, including interferon-α2a, may be considered while bridging to transplantation.[389]

Amphetamine-methamphetamine exposure should be a part of the history for all children with potential exposure. In the case of methamphetamine-induced PAH, therapies currently approved for other forms of group 1 PAH should be used according to the disease severity at presentation. Removal of the inciting drug or toxin is critical as soon as the diagnosis is made. Multiple studies have highlighted the occurrence of PAH in current and former cocaine users.[390,391] Despite the widespread use of various compounds that may serve as central nervous system stimulants for attention deficit–hyperactivity disorder, including dexmethylphenidate, no studies have addressed whether there is an association between attention deficit–hyperactivity disorder treatments and PAH in children.

9.1. Prognosis

Before the era of targeted PH therapies, most children with IPAH died within 1 to 2 years of diagnosis, whereas adults had a median survival of 2 to 3 years. Morbidity and mortality rates vary and depend on the age, the degree of PH, the subtype, and the response to vasodilator therapy. Death may occur as a result of both acute and chronic right-sided heart failure and its associated arrhythmias. Additionally, patients can be affected by the complications associated with low cardiac output. Children who respond to short-term vasodilator drug testing have a 5-year survival rate of 90%, whereas children who do not initially respond have a 5-year survival rate of 33%.

Recommendations

1. **Lung biopsy may be considered for children with PAH suspected of having pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or vasculitis (*Class IIb; Level of Evidence C*).**
2. **Referral to lung transplantation centers for evaluation is recommended for patients who are in WHO functional class III or IV on optimized medical therapy or who have rapidly progressive disease (*Class I; Level of Evidence A*).**
3. **Referral to a lung transplantation center for evaluation is recommended for patients who have confirmed pulmonary capillary hemangiomatosis or PVOD (*Class I; Level of Evidence B*).**

10. Pediatric Heart Disease

10.1. PAH With Systemic-to-Pulmonary Shunt

PAH is a common complication of CHD and contributes to substantial morbidity and mortality.[392] The patient's age and type of lesion strongly contribute to the risk of developing irreversible PVD. In general, pressure overload and conditions with high flow such as occurs with large VSDs are more likely to cause PAH than low-pressure, high-flow lesions such as ASDs. Early diagnosis and surgery have dramatically decreased the development of late PAH and the propensity for postoperative PHCs (see below). In general, patients with a VSD or PDA do not develop irreversible pulmonary vascular changes before 9 months to 2 years of age,[393] but surgery is generally recommended sooner. Without appropriate surgery, an estimated 50% of patients with a large, nonrestrictive VSD will develop ES.[394]

Patients with an ASD are less likely to develop severe PAH, which usually occurs in the third to fifth decade. The incidence of PH in patients with an ASD is 6% to 17%[395]; PAH persisting after ASD closure is more likely in older patients with larger defects.[396] Infants with an ASD or a VSD with concomitant chronic lung disease are at an increased risk for the early development of severe PVD and complications after cardiac surgery.[397] The presence of resting cyanosis (oxygen saturation <90%) is worrisome because it predicts risk of elevated PVR and death after closure of the defect.[395]

In the EuroHeart survey of adults with CHD, hemodynamics at follow-up were worse in nonoperated patients with ASD than in the patients whose defects had been closed, especially those with moderate or large defects.[398] In adults with small ASDs, patients generally did well, and an operation was deemed unnecessary.[398] ES in adults with ASD was rare, occurring in 15 of 896 patients (2%).[399] However, the risk of PAH with a sinus venosus ASD is likely higher than that of a secundum ASD.[395,400] Patients with cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, and univentricular heart with high pulmonary blood flow and those with Down syndrome with or without large left-to-right shunt (eg, atrioventricular canal defects)

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are at highest risk of rapidly developing irreversible PVD. Palliative shunting operations for certain cardiac anomalies such as the Waterston or Potts anastomosis, which increases pulmonary blood flow, may also lead to the subsequent development of PH.

10.2. Single-Ventricle Physiology

Cavopulmonary anastomoses, namely bidirectional Glenn shunts and Fontan baffles, are used to treat children whose CHD precludes direct repair often due to a hypoplastic ventricle repair.[401] After cavopulmonary surgery, systemic venous return drains directly into the pulmonary arteries, and the pulmonary circulation is without a dedicated subpulmonary ventricle. The systemic and pulmonary circulations are in series, and pulmonary blood flow is dependent on the transpulmonary gradient and kinetic energy imparted by systemic ventricular contraction.[402,403] The state of the pulmonary vascular bed strongly influences outcome in patients undergoing cavopulmonary anastomosis because small elevations of PVR can markedly impair cardiac performance.[404,405] Selected patients with increased PVR have been treated with sildenafil and bosentan. Bosentan improves exercise tolerance and oxygen saturation in some patients with impaired hemodynamics after Fontan surgery.[406] A single dose of sildenafil improves $\dot{V}o_2$ and pulmonary blood flow in patients after the Fontan anastomosis.[365] A randomized, crossover trial showed that sildenafil therapy improved exercise tolerance and ventilatory efficiency after 6 weeks, but PVR was not directly assessed.[366]

Measurements of transpulmonary gradient and PVRI are important in the selection of patients with a single ventricle for cavopulmonary surgery, and even small increases in these parameters adversely affect survival.[407–409] A transpulmonary gradient >6 mm Hg and PVRI >3 WU·m^2 have been suggested as predicting high risk for poor outcomes in these patients. However, many problems persist in estimating pulmonary blood flow and PVR after cavopulmonary anastomoses. These include poor reliability of pressure measurements in a nonpulsatile system, sampling a true pulmonary artery saturation in the presence of aortopulmonary collaterals or residual forward flow from the ventricles, and the effect of venous collaterals or arteriovenous malformations that "steal" blood flow from the pulmonary circulation. Late attrition after cavopulmonary anastomosis is related to increased PVR. Additionally, such complications as plastic bronchitis, protein-losing enteropathy, and decreased exercise tolerance may be the consequences of high PVR.[403,406,407,410]

10.3. Operability

In the child with CHD and PVD, determination of baseline hemodynamics and reactivity to vasodilators is crucial for selecting surgical candidates who will likely have successful short-term and long-term outcome.[84,117,411] One of the most important factors in long- term survival and freedom from PVD is the age at which surgery is performed.[412] Children who underwent surgical repair before 9 months of age, regardless of the preoperative Heath-Edwards scores of vascular morphology or hemodynamic parameters, had normal PAP 1 year after surgery. However, certain lesions such as d-transposition of the great arteries, complete atrioventricular septal defect, and truncus arteriosus are more prone to the early development of severe PVD.[412,413] In general, surgery in the child with CHD is recommended before 2 years of age,[393,414] but most centers will perform complete repair of lesions within the first months of life.

Cardiac catheterization provides an assessment of PVR, PVR-to-SVR ratio, and pulmonary-to-systemic blood flow. However, determination of pulmonary hemodynamics in these patients can be controversial. Preoperative PVR and reactivity in patients with CHD can be difficult to ascertain.[117] Acute hemodynamic evaluation of these patients provides a snapshot that may not accurately represent their overall clinical status. Cardiac catheterizations are frequently performed under general anesthesia, which may lower systemic arterial blood pressure.[415] Furthermore, measurements of $\dot{V}o_2$ in children with CHD are problematic and frequently based only on estimates. The LaFarge equation can overestimate $\dot{V}o_2$ in ventilated patients with CHD of all ages, but particularly in children <3 years of age.[91,416] Estimates rather than direct measurements of Po_2 in the pulmonary artery can further overestimate pulmonary blood flow and underestimate PVR.

Past studies have evaluated pulmonary hemodynamics to determine operability, yet precise values that best correlate with early and late outcome remain unclear. Many studies are not directly comparable because of differences in sedation and the use of measured or assumed $\dot{V}o_2$. The first Natural History Study of VSD concluded that no child repaired before 2 years of age, regardless of the initial PVR-to-SVR ratio, had an elevated PVR-to-SVR ratio 4 to 8 years after surgery.[414] In children with a large VSD, a positive preoperative response to oxygen, as defined by a decrease in the PVR-to-SVR ratio ≥30%, did not correlate with either operative survival or late PVR-to-SVR ratio.[116] Children with PVR >6 U·m^2 have a poor prognosis regardless of their lung morphology, and some patients with low Heath-Edwards scores (grade I or II) can still have high PVR.[116] Studies of children and young adults with VSD reported successful surgical outcomes in patients with preoperative PVR <8 U·m^2.[108,417] A positive AVT response with short-term exposure to iNO in children with higher baseline PVR may predict beneficial outcomes after surgery.[111,418] Six of 7 children with CHD and baseline PVR >6 U·m^2 and PVR-to-SVR ratio >0.3 who responded to brief iNO inhalation with a decrease in PVR and PVR-to-SVR ratio >10% and an absolute PVR-to-SVR ratio <0.3 survived surgical intervention.[418] Several studies suggest that a PVRI <7 to 8 WU·m^2 in response to a vasodilator challenge predicts a good outcome,[108,411,417,419] although good surgical outcomes can occur with higher PVR in some settings.

A modification of an algorithm originally described by Lopes[420] is presented for patients with simple shunts such as an ASD, a VSD, or a PDA in Figure 4. Patients who are <1 year of age with simple shunts and evidence of pulmonary overcirculation with exclusive left-to-right shunting by echocardiography and saturations on room air >95% do not necessarily need to undergo cardiac catheterization before surgery. However, it is prudent for older patients to undergo catheterization before surgery. Likewise, patients with more complex disease such as truncus arteriosus who present after

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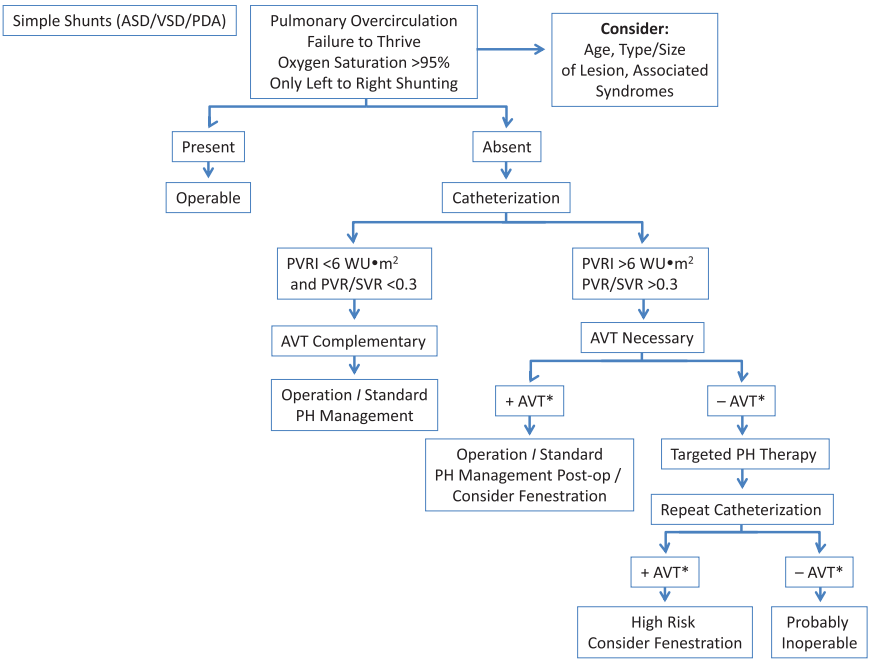

Figure 4. Assessment of operability for shunt lesions in patients with congenital heart disease and pulmonary hypertension (PH). ASD indicates atrial septal defect; AVT, acute vasoreactivity testing; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SVR, systemic vascular resistance; VSD, ventricular septal defect; and WU, Wood units. *PVRI <6 WU·m^2 and PVR/SVR <0.3. Modified in part from Lopes and Bart[420a] with permission.

the first several months of life also may benefit from catheterization. Those patients who are older and are hypoxemic with bidirectional shunting may benefit from vasodilator testing to stratify risk. Many programs advocate for a fenestration at the atrial or ventricular level in patients with higher PVR. The role of longer-term "treatment and repair" and a period of pulmonary artery banding remain controversial and are less well defined.[421] The algorithm presented takes a conservative approach because the upper limits of operability are poorly defined.

10.4. Eisenmenger Syndrome

ES describes PAH in the setting of CHD with a reversed central shunt resulting from marked elevation of PVR and bidirectional or right-to-left shunting through a systemic-to-pulmonary connection, leading to cyanosis and erythrocytosis.[422] In general, the prognosis of patients with ES is much better than for patients with IPAH, but syncope, right-sided heart failure, and severe hypoxemia are similarly associated with a poor prognosis.[423] However, prognosis for children with ES may be worse than previously suggested as a result of a survival bias in adult series.[106] ES associated with complex heart disease leads to earlier clinical deterioration and death compared with ES related to an ASD, a VSD, or a PDA.[424–426] Patients with ES have more favorable RV function until the late stages of PVD, whereas patients with late repair of CHD who subsequently develop PAH tend to do poorly, suggesting that RV performance is critical for survival. Morbidity in ES is high and includes hemoptysis, pulmonary thromboembolism, stroke, and cerebral abscess. Maternal death is estimated at 50% in women with ES during pregnancy. Children with ES are at risk for sudden death.[427,428] Data from children with severe PAH before PAH-specific therapy suggest a dismal survival of 12% at 1 to 2 years.[429]

Survival may have improved with the availability of PAH-specific drug therapies, but this is based on the flawed approach of comparing a modern cohort with historical controls rather than direct RCTs.[105,342,367] Survival of patients in the UK network for IPAH was 92%, 84%, and 72% at 1, 3, and 5 years, respectively. Transplantation-free survival for this population was 89%, 76%, and 57% at 1, 3, and 5 years. Children with associated PAH have survivals of 92%, 84%, and 57% at 1, 3, and 5 years. Survival in this group was dependent on diseases associated with PH, with postoperative CHD and connective tissue disease (CTD) having the worst survival.[104,105]

Conventional therapies such as digitalis, diuretics, anticoagulants, iron supplementation, and oxygen therapy are often used, yet these strategies have not been shown to improve survival.[426,420] Nocturnal oxygen therapy in ES does not appear to alter long-term outcome.[430] Iron therapy improves exercise capacity and quality of life, and red blood cell depletion may provide temporary relief from major hyperviscosity symptoms in ES.[431] PAH-specific therapy for ES has evolved over the past decades.[388,376,432] In a randomized, placebo-controlled trial of ES patients in WHO functional class III, bosentan therapy reduced PVR and mPAP and increased 6MWD by 53.1 m without worsening gas exchange.[288] Children but not adults with ES developed a progressive decline in exercise capacity during prolonged bosentan therapy.[349] Sildenafil therapy improves functional class and hemodynamic parameters in patients with ES.[433] A retrospective study recently reported that the use of PAH-specific therapies, including PDE5 inhibitors, prostanoids, and ERAs, improved survival in adult ES patients in functional class III and IV.[432]

10.5. Left-Sided Heart Disease

CHD and acquired and congenital cardiomyopathies are common causes of pulmonary venous hypertension in children. However, LV diastolic dysfunction is emerging as an important cause of late PH in older children with CHD, especially after repair of coarctation of the aorta, VSD repairs, cardiac transplantation, supra-annular mitral valve replacement, and

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hypoplastic left heart syndrome and its variants, including Shone syndrome.[434,435] In pulmonary venous hypertension, iNO can decrease the transpulmonary gradient and PVRI with or without a decrease in PAP, depending on the cause of the pulmonary venous hypertension.[111,118,436] Although testing with iNO is useful, pulmonary edema can develop in patients with pulmonary vein obstruction, mitral stenosis, or reduced LV ejection fraction.[436,437] The histopathology of pulmonary venous hypertension includes medial thickening of pulmonary arteries and veins and, less commonly, intimal fibrosis of veins and arteries in children.[438,439]

10.6. Hypoplastic Left Heart Syndrome

Pulmonary vascular changes resulting from LA hypertension contribute adversely to the presentation and outcome of patients with hypoplastic left heart syndrome.[440,441] Severe flow restriction or intact atrial septum in hypoplastic left heart syndrome is associated with profound cyanosis, pulmonary artery hypoplasia, lymphangiectasis, and high mortality despite aggressive therapy.[442,443] In neonatal survivors, persistent pulmonary vascular changes may compromise subsequent palliation.[444] However, mild flow restriction at the foramen ovale may reduce pulmonary blood flow and systemic steal and permit a degree of preoperative stability. In the postoperative patient, an adequate AS is extremely important to permit adequate oxygenation and subsequent progression to cavopulmonary anastomosis.

10.7. Mitral Stenosis

Children with mitral stenosis generally have reactive pulmonary vascular beds.[435,445] PH after relief of mitral valve stenosis, whether by valve replacement or valvotomy, reduces PAP to near-normal levels during short- and long-term follow-up.[446,447] The best pulmonary vascular response after mitral valvuloplasty or replacement occurs in patients with acquired mitral stenosis or isolated congenital mitral stenosis without additional left-sided obstructions or intracardiac shunts.[448] In children, diuretic therapy may result in a marked improvement in symptoms, mitral pressure gradient, and PAP.

In children with hypoplastic left heart syndrome variants, regression may not occur despite relief of the transmitral valve pressure gradient as a result of other anatomic factors that elevate LA pressure, including residual LV outflow tract obstruction; elevated LV end-diastolic pressure caused by a small, hypertrophied LV; endocardial fibroelastosis; and a small, noncompliant LA.[435] Long-term outcome is affected by the degree of residual mitral stenosis, the presence or absence of a true parachute mitral valve, LV hypoplasia, and the need for multiple surgical reinterventions, which lead to further LV diastolic dysfunction. In children with Shone syndrome, severe PH was associated with poor outcomes. However, a recent report with 5- and 10-year survival rates of 88% and 83% suggests that elevated PVR is not a major issue in midterm survivors.[449]

10.8. Aortic Stenosis

PVD associated with aortic stenosis occurs secondary to LV diastolic abnormalities that increase LA and pulmonary venous pressures. The transpulmonary gradient is initially normal but increases over time as a result of augmented vasoconstriction and vascular remodeling.[450] In aortic stenosis, LV hypertrophy initially lowers wall stress and compensates for increased LV afterload. However, changes in LV wall remodeling subsequently impair relaxation in early diastole and decrease compliance in mid to late diastole, leading to LV diastolic dysfunction.[451]

There are important differences between acquired and congenital aortic valve stenosis with regard to the LV and pulmonary vascular bed. Most patients with acquired aortic stenosis or postneonatal onset of LV outflow tract gradients have normal LV size, and the pulmonary vascular bed has undergone normal postnatal remodeling. In contrast, critical aortic stenosis or aortic atresia in fetuses and newborns is associated with increased pulmonary vascular muscularization, and pulmonary veins become arterialized. These changes are present in utero and may impair postnatal pulmonary vascular adaptation and development.[452] Decreased LV size may impose additional diastolic abnormalities not seen in acquired aortic valve stenosis. After successful aortic balloon valvotomy in newborns, the LV remodels and grows toward normal values by 1 year of life.[453] Outcome for infants born with critical aortic valve stenosis has improved steadily, and 5-year survival rates are between 77% and 85% at 5 years.[454,455] The risk of sudden death in children after balloon aortic valvuloplasty is highest in infants with elevated PAP beyond 1 month of age.[453] PH can persist throughout childhood in some patients 4 to 12 years after treatment of congenital aortic valve stenosis in infancy. LV diastolic dysfunction contributes significantly to PH in these children. Interestingly, echocardiographic evidence of LV diastolic dysfunction is common in patients with biventricular circulation after fetal aortic valvuloplasty and persists in short-term follow-up.[456]

10.9. Pulmonary Vein Stenosis

Pulmonary vein stenosis is a particularly vexing problem and often contributes to poor outcomes. Despite surgical, medical, and catheter-based attempts, therapies for pulmonary vein stenosis are often ineffective, with recurrence of disease and no cure.[273,457,458] Sutureless repair of pulmonary vein stenosis after repair of total anomalous pulmonary venous return is more likely to be successful than in native pulmonary vein disease.[459,460]

Recommendations

1. **In children with significant structural heart disease (ie, ASD, VSD, and PDA) who have not undergone early repair (as generally defined by age of 1 to 2 years, depending on the lesion and overall clinical status), the following are recommended:**
   a. **Cardiac catheterization should be considered to measure PVRI and to determine operability (*Class II; Level of Evidence B*).**
   b. **Repair should be considered if PVRI is <6 WU·m² or PVR/SVR <0.3 at baseline (*Class I; Level of Evidence B*).**

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2. **In children with evidence of right-to-left shunting and cardiac catheterization revealing a PVRI ≥6 WU·m² or PVR/SVR ≥0.3, repair can be beneficial if AVT reveals reversibility of PAH (absolute PVRI <6 WU·m² and PVR/SVR <0.3) (*Class IIa; Level of Evidence C*).**
3. **If cardiac catheterization reveals a PVRI ≥6 WU·m² or PVR/SVR ≥0.3 and minimal responsiveness to AVT, the following are recommended:**
   a. **Repair is not indicated (*Class III; Level of Evidence A*).**
   b. **It is reasonable to implement PAH-targeted therapy followed by repeat catheterization with AVT after 4 to 6 months and to consider repair if the PVRI is <6 WU·m² (*Class IIb; Level of Evidence C*).**

11. PHCs/Acute RV Failure

Studies of the pathophysiology and management of acute PHCs in critical care settings have focused mainly on the perioperative period after CHD surgery and cardiac and lung transplantation. As in all forms of PHVD, RV adaptation to an increased afterload rather than the absolute PAP or PVRI determines symptoms and outcome. PHCs are sudden and potentially lethal increases in PAP and PVR that cause acute right-sided heart failure accompanied by systemic hypotension, myocardial ischemia, and, at times, bronchoconstriction[461,462] (Figure 5). PHCs can be triggered by various stimuli, including pain, anxiety, tracheal suctioning, hypoxia, and acidosis, and often occur after successful surgery. Although most commonly described after cardiac surgery, PHCs can also accompany rapid withdrawal of PH-specific therapy[463,464] and may be precipitated outside the perioperative period by intercurrent illness or noncardiac interventions such as acute lung injury or infection.[79,465,466]

The diagnosis of postoperative PHC is based on the following findings: a sudden increase in PAP, followed sequentially by increased RA and RV end-diastolic pressures, decreased systemic and mixed venous oxygen saturations, decreased systemic pressure, and decreased cardiac output. Bronchoconstriction or increased airway resistance may accompany these hemodynamic changes.[467] A composite hemodynamic definition of a major PHC includes a sudden increase in the ratio of PAP to systemic artery pressure >0.75 that is often accompanied by an increase in central venous pressure >20%, a decrease in systemic blood pressure >20%, and a decrease in systemic oxygen saturation >90% with signs of low cardiac output.[462] PA catheterization is useful for the diagnosis and management of PHCs, and without direct measurements of pulmonary hemodynamics, the diagnosis of PHC is imprecise and may commit a child to a course of unnecessary therapy for PH or delay investigation of the correct diagnosis.

In contrast to the high morbidity of PA catheters in adults and other intensive care unit settings,[468] the use of PA catheters for monitoring children after cardiac surgery has been associated with low morbidity.[469] However, as PHCs have become less frequent, the use of PA catheters has decreased in clinical practice. The routine use of PA catheters in populations with a low risk for PHC may delay patient recovery and prolong intensive care unit stay without clear benefits. Furthermore, evidence-based guidelines on the values of PAP or PVRI that indicate the need for postoperative therapy are lacking. Patients with postoperative mPAP >25 mmHg or a ratio of PAP to systemic artery pressure >60%, especially with signs of low cardiac output or hemodynamic instability, are concerning and may indicate a need for intervention. Although accurate echocardiography is challenging during PHC, its use is very helpful to identify at-risk patients with elevated RV pressures in the postoperative period. Echocardiography is also useful to evaluate residual shunts, additional or overlooked cardiac lesions, proximal RV or pulmonary artery obstruction, atrioventricular valve dysfunction, and ventricular performance that may contribute to PHCs. Better noninvasive, real-time, accurate assessments of PAP and RV function that are suitable for use in unstable patients are clearly needed.

11.1. Epidemiology of Acute Postoperative PH

PH is identified as a major contributor to postoperative hospital length of stay, requirements for prolonged mechanical

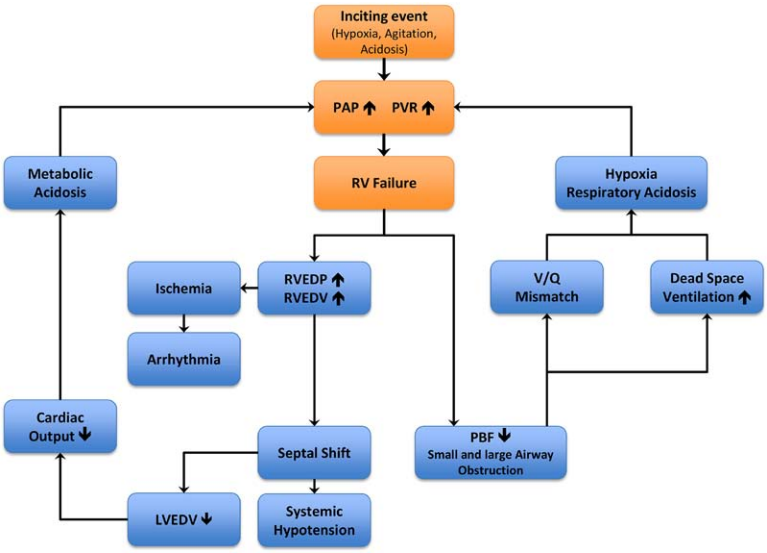

Figure 5. Mechanisms of acute right ventricular failure and pulmonary hypertensive crisis. LVEDV indicates left ventricular end-diastolic volume; PAP, pulmonary arterial pressure; PBF, pulmonary blood flow; PVR, pulmonary vascular resistance; RVEDP, right ventricular end-diastolic pressure; and RVEDV, right ventricular end-diastolic volume.

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ventilation support, and postoperative mortality.[470] The incidence of postoperative PHC has decreased from 31% to 6.8% even before the routine use of PH-specific therapies.[471] The reduction in the incidence of PHCs may be due to a combination of surgical intervention at a younger age; the submission of more robust surgical candidates; improvements in surgical techniques, especially the conduct of cardiopulmonary bypass and postbypass ultrafiltration; improved understanding of the pathophysiology; and the availability of safe pulmonary specific vasodilators.[471–476] Currently, PH complicates 2% to 7% of patients undergoing congenital cardiac surgery, with PHCs occurring in 0.75% to 4% of patients.[477,478] PHCs account for a mortality rate of 8% within the first month after repair of total anomalous venous connection, and PHC episodes are strongly associated with high risk for late death.[479,480] Mortality from PHC has varied from 20% to 50% in older studies, with a more recent estimate of 20%.[475]

11.2. Pathophysiology of Postoperative PH

Risks for PHC include the age of the patient, the type of cardiac lesion, and abnormal pulmonary vascular development in children with CHD. Patients with truncus arteriosus, transposition of the great arteries, obstructed total anomalous pulmonary venous connection, or aortic origin of pulmonary artery are especially predisposed to PHC, especially if repair is delayed beyond the neonatal period.[481,482] In addition, LA or pulmonary venous hypertension increases pulmonary vasoreactivity and the risk for postoperative PHCs.[445] Patients with CHD and genetic syndromes, chromosomal abnormalities, or extracardiac anomalies have a high incidence of lung hypoplasia, and their difficult postoperative courses may be complicated by a simplified pulmonary vascular bed.[182,254,483]

In addition to perioperative factors that directly alter the pulmonary circulation and predispose to PH, the effects of surgery itself can further impede hemodynamic tolerance for increases in PVR. For example, closure of a VSD or ASD may impair adaptation to withstand sudden postoperative increases in PVRI. Preoperatively, cardiac output may be maintained through decompression via the cardiac shunt, but after closure, the RV must carry the whole burden of an elevated PVRI. The response of the RV to an increase in PVRI is influenced by the preoperative RV function and postoperative factors such as right ventriculotomy, transient myocardial dysfunction, tricuspid valve and pulmonary valve regurgitation, and the loss of sinus rhythm. If RV pressure in systole and diastole rises above aortic pressure, coronary perfusion is impaired, causing cardiac ischemia and dysfunction, which can be improved by increasing SVR in experimental models.[484,485]

11.3. Treatment of Postoperative PH

Postoperative challenges from patients with nonreactive PVD differ from those with a more reactive pulmonary vascular bed. Positive AVT in this setting is defined as a 20% decrease in mPAP and PVRI in response to acute testing with a pulmonary vasodilator (as discussed above). In nonresponders, closure of shunt lesions prevents the RV from decompressing, increasing risk for RV failure that may require temporary mechanical support.[486,487] The unidirectional flap valve for VSD or ASD closure permits intermittent right-to-left shunting and preserves LV preload and cardiac output in settings of nonreactive PH or RV failure.[488,489] Pulmonary artery banding has been used to protect the pulmonary vascular bed from excessive pressure and flow in patients who are at a high risk for primary repair or need time to mature before undergoing cavopulmonary anastomosis. However, interstage mortality is high for patients with correctable biventricular lesions.[490] PVD, even in the presence of advanced structural remodeling, may regress after banding,[491,492] but pulmonary artery banding in patients with an increased PVRI has not found a routine place in therapy.[493,494]

Respiratory management plays a critical role in the management of PH and avoidance of PHCs. Maintaining adequate lung volumes (functional residual capacity) and gas exchange while avoiding acidosis during the postoperative period is crucial for successful outcomes.[83] Pulmonary edema, atelectasis, ventilation-perfusion mismatch, and bronchoconstriction after cardiac surgery increase PVR. High doses of fentanyl attenuate the stress response in neonates undergoing surgery,[495] and continuous fentanyl infusion with the use of muscle relaxants is recommended during the early postoperative period. Supplemental doses of fentanyl immediately before endotracheal suctioning are often used to attenuate the risk for PHCs in postoperative patients. Because acute hypercarbia with acidosis can abruptly increase PVR and impair RV performance, avoiding acidosis may be important for the prevention of pulmonary vasoconstriction and PHCs. Brief hyperventilation or sodium bicarbonate infusions are useful for the immediate management of PHC as more specific strategies are initiated.[84] However, prolonged alkalosis may have adverse effects because hyperventilation can induce lung injury and the pulmonary vasodilator response to sodium bicarbonate infusions may be transient. Sodium bicarbonate can also decrease cardiac output and cerebral blood flow and increase central venous pressure and SVR.

11.4. PAH-Specific Drug Therapy of Acute Postoperative PH

The primary goal of PAH-specific drug therapy is pulmonary vasodilation and enhancing RV function and cardiac output while avoiding adverse effects such as systemic hypotension and hypoxia. Management of symptomatic PH involves early identification and close monitoring of high-risk patients and avoiding or mitigating vasoconstrictive triggers, in conjunction with the use of pulmonary vascular–specific therapies. Because of such advantages as a selective pulmonary vasodilator, ease of administration, and rapid onset of effect, iNO has become an accepted standard therapy for postoperative PH.[496] Unlike nonselective pulmonary vasodilators, iNO at low doses improves ventilation-perfusion matching, decreases intrapulmonary shunt fraction, and often improves systemic arterial oxygenation, especially in the setting of lung disease.[465]

In an RCT of children after cardiac surgery, iNO treatment reduced episodes of PHC and shortened the time to reach criteria for extubation.[497] However, the duration of mechanical ventilation was not different with iNO therapy, likely because of the study protocol used for slow weaning of iNO. Other studies have demonstrated selective reduction of

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PAP in children after cardiopulmonary bypass[498] and that iNO may reduce mortality after repair of atrioventricular septal defects.[499] Several small observational studies suggest benefits of iNO therapy in postoperative children with PH. However, another randomized trial of postoperative CHD failed to show benefit with iNO therapy.[500]

iNO is commonly used to treat postoperative PH in patients with CHD at doses between 2 and 80 ppm. Doses of iNO >20 ppm rarely have additional benefit on PH, and lower doses (<10 ppm) are useful for improving gas exchange. As observed in newborns with PPHN, rapid withdrawal of iNO therapy can cause rebound PH, which is defined as a >20% increase in PAP with a ratio of PAP to systemic artery pressure >0.6 associated with decreased cardiac output, hypotension, or systemic desaturation. Rebound PH can be minimized by a slow reduction of iNO doses <1 to 5 ppm before therapy is stopped,[367] but this can delay time to extubation. Hemodynamically stable patients can often tolerate extubation and switching to noninvasive delivery of iNO by nasal cannula.[256]

A randomized, controlled study has shown that oral sildenafil attenuates rebound PH after iNO withdrawal and shortens the time to extubation and the length of time that intensive care is needed.[371] Dipyridamole has also been used to attenuate rebound after withdrawal of iNO therapy.[369] For patients with PH, intravenous[475] or orally administered[367] sildenafil and inhaled iloprost, PGI_2, nitroglycerine, or milrinone and intravenous PGI_2 may enhance iNO-induced pulmonary vasodilation.[501] The short-term effects of inhaled PGI_2, milrinone, and nitroglycerin may be as effective as iNO at lowering PVRI and improving intrapulmonary shunt fraction with minimal decreases in systemic hemodynamics.[294,501–504] In a placebo-controlled trial, intravenous sildenafil reduced PAP and shortened the time to extubation and intensive care unit stay without adverse events in children after cardiac surgery.[475] A randomized, prospective trial in children compared intravenous sildenafil with iNO therapy and reported augmentation of pulmonary vasodilation with combined treatment. However, intravenous sildenafil can cause systemic hypotension and reduce oxygenation, especially with lung disease.

Compared with iNO, intravenous sildenafil has a greater vasodilator response but increased intrapulmonary shunt in postoperative patients.[114] Drugs that augment cardiac output and dilate the pulmonary vascular bed such as milrinone, levosimendan, and nesiritide may be useful adjuncts, provided that the patient can tolerate systemic vasodilation.[505] Vasopressin is a pulmonary vasodilator and systemic vasoconstrictor that may be useful for the treatment of systemic hypotension associated with PH.[506] Preoperative oral sildenafil treatment did not decrease PVRI in children after surgery and mildly decreased ventricular function and oxygenation in an RCT.[507] However, children selected for this study did not have PH before surgery. A randomized study of sildenafil therapy for 1 week before and after surgery demonstrated that the pretreatment regimen was superior to the course of oral sildenafil that was started at surgery and for 1 week postoperatively. Compared with initiation of sildenafil treatment at surgery, longer pretreatment with sildenafil decreased mPAP, time on cardiopulmonary bypass, and duration of intensive care unit and hospital days.[508]

11.5. ECMO, AS, and Lung Transplantation

PAH-specific therapies have dramatically changed the management of children and adults with severe PH, and advances in medical management have improved survival and quality of life. However, some patients fail to respond to the drug and related therapies, and disease progression leads to severe RV dysfunction. AS and lung transplantation represent potential therapeutic options for these patients. In the setting of RV failure caused by severe PAH, AS provides an iatrogenic interatrial communication to sustain cardiac output and oxygen delivery despite worsening oxygenation caused by extrapulmonary right-to-left shunting of blood. The rationale for AS in the setting of severe PAH is based partly on experience that patients with CHD and shunt lesions have better survival than patients with IPAH. Published experience with AS has been relatively limited to case series and observational reports.[509–514] Overall, AS acutely increases cardiac output and often leads to sustained improvements in functional class, 6MWD test, functional class, and quality of life. AS has been used successfully as a bridge to lung transplantation.

In nearly all cases, AS is performed late in the clinical course after the failure of medical treatment. A recent retrospective series examined the effects of AS in severe PAH earlier in the course, before initiation of PAH-specific drug therapy.[515] This analysis reported outcomes of patients with severe PAH (mean age, 35 years) who had received septostomy alone or combined with drug therapy on survival. AS was the only form of treatment in 21 patients, whereas 11 received additional pharmacotherapy after AS. In patients receiving 50 procedures, there was 1 procedure-related death resulting from severe hypoxemia, and 21 patients died during follow-up. Median survival for the overall group was 60 months, with patients who received AS alone surviving on average 53 months (95% confidence interval, 39–67) compared with 83 months (95% confidence interval, 57–109) for those who received drug therapy with AS (log-rank 6.52; P=0.010). These findings suggest that in selected patients AS is a safe intervention and that survival improves when AS is combined with PAH-specific pharmacotherapy. Overall, AS should be considered only in selected patients, and procedures should be performed by experienced cardiologists at PH centers and may be considered as a bridge to lung transplantation.

Lung transplantation is often the only therapeutic option for eligible patients with advanced PAH and RV failure who continue to deteriorate despite optimal medical management. Current international registry data suggest that 3.2% of lung transplantations in adults are performed for severe PAH, with nearly all being bilateral lung transplantations, and a reported 50% 5-year survival.[516,517] Predictors of poor prognosis in PAH, including advanced functional class with adverse pulmonary hemodynamics at right-sided heart catheterization despite aggressive treatment, should prompt early referral for transplantation. Double-lung transplantation is generally recommended for IPAH, and heart-lung transplantation is reserved for selected IPAH patients or those with CHD with complex anatomic disease or ES. AS and novel strategies, including lung assist devices or conduits from the pulmonary artery to the LA, can be considered as a bridge to transplantation for patients with rapid clinical decline. Improving transplantation

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outcomes in younger children with diffuse lung diseases and other disorders are encouraging, but considerable early and late morbidities persist.[518]

There is extensive experience with the use of ECMO for the resuscitation of children after cardiopulmonary collapse or with low cardiac output, including children with PHVD. Experience suggests that earlier consideration of mechanical cardiopulmonary support is indicated in children with PVHD who are failing medical therapy or after cardiac arrest.[81,486,487] Technological advances in ventricular pumps and oxygenators make support of children with ECMO over prolonged periods attainable, and the advent of efficient centrifugal external and even smaller implantable devices will make transition from ECMO to support with ventricular assist devices either as a bridge to transplantation or for prolonged therapy.[519,520] A retrospective study described relatively poor outcomes of children with PH who required ECMO support immediately before lung transplantation, with only 2 of 19 patients (18%) surviving to 1 year of age.[521]

Successful use of the Berlin Heart EXCOR ventricular assist device combined with PAH-specific drug therapy has been reported in successful bridging to cardiac transplantation of 2 children with severe PH caused by LV failure.[519] For patients with PHVD who are predicted to have adequate or recoverable cardiac function, successful use of a pumpless lung assist membrane device has been reported for the temporary support in 2 children with PHVD.[522–524] This device may have particular application to patients with PVOD.

Recommendations

1. **General postoperative strategies for avoiding PHCs, including the avoidance of hypoxia, acidosis, and agitation, should be used in children at high risk for PHCs (*Class I; Level of Evidence B*).**
2. **Induction of alkalosis can be useful for the treatment of PHCs (*Class IIa; Level of Evidence C*).**
3. **Administration of opiates, sedatives, and muscle relaxers is recommended for reducing postoperative stress response and the risk for or severity of PHCs (*Class I; Level of Evidence B*).**
4. **In addition to conventional postoperative care, iNO or inhaled PGI_2 should be used as the initial therapy for PHCs and right-sided heart failure (*Class I; Level of Evidence B*).**
5. **Sildenafil should be prescribed to prevent rebound PH in patients who have evidence of a sustained increase in PAP on withdrawal of iNO and require reinstitution of iNO despite gradual weaning of iNO dose (*Class I; Level of Evidence B*).**
6. **In patients with PHCs, inotropic/pressor therapy should be used to avoid RV ischemia caused by systemic hypotension (*Class I; Level of Evidence B*). Mechanical cardiopulmonary support should be provided in refractory cases (*Class I; Level of Evidence B*).**
7. **AS is recommended for patients with RV failure, recurrent syncope, or PHCs that persist despite optimized medical management but must be performed in an experienced PH center (*Class I; Level of Evidence B*).**

12. Lung Diseases

Developmental disorders of the lung with associated PAH may be genetic in origin or may be due to events during fetal or early postnatal lung development, often with accompanying lung hypoplasia (Table 9). These disorders most commonly present at birth or in the first months to years of life, and the most common disorders are BPD and CDH. ACD is a rare but fatal disorder of early infants in which there is disordered alignment of pulmonary veins and a profound underdevelopment of the alveolar capillaries.[525] Recently, the clinical spectrum and associated gene abnormalities associated with ACD have been described.[526,527] With identification of *FoxF1* as a genetic marker for many infants with ACD, genetic studies may precede the need for lung biopsy for definitive diagnosis of ACD if time permitted. Although there are case reports of survival for weeks to months with PAH pharmacotherapy,[528] the natural history of ACD is usually relentless, and lung transplantation is the only potential route to long-term survival.

Surfactant protein dysfunction syndromes are increasingly recognized as the cause of severe, prolonged respiratory failure in young, usually full-term infants with diffuse lung infiltrates on chest radiograph or chest CT scan. These syndromes have been associated with homozygous mutations in surfactant protein B deficiency, ABCA3 and thyroid transcription factor 1 mutations, and heterozygous mutations in surfactant protein C. Although PH has been described as an associated finding,[529,530] the largest published series of patients described with these disorders do not describe PAH either by clinical testing or as a notable part of the histopathology.[531–533] There have been case reports of PAH in association with certain of these disorders but no description of the use of PAH pharmacotherapies.[534]

Scimitar syndrome includes hypoplasia of the right lung, total or partial anomalous pulmonary venous return of the right lung, dextroposition of the heart, and right pulmonary artery hypoplasia. In its infantile form, it is often associated with PAH, the cause of which is usually multifactorial.[535] PAH is associated with significant morbidity and mortality in

Table 9. Developmental Lung Diseases Associated With PH

Bronchopulmonary dysplasia
Congenital diaphragmatic hernia
Alveolar capillary dysplasia with misalignment of veins
Lung hypoplasia
Surfactant protein abnormalities
SPB deficiency
SPC deficiency
ABCA3
TTF-1/Nkx2
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

PH indicates pulmonary hypertension; SPB, surfactant protein B; and SPC, surfactant protein C.

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scimitar syndrome, is associated with congenital heart defects, and usually presents early in infancy with right lung hypoplasia or pulmonary vein stenosis and systemic collaterals from the aorta.[536] Intracardiac defects are the most common anomalies associated with this syndrome, with a prevalence of 40%. Treatment of PAH associated with scimitar syndrome has largely been restricted to surgical and catheter-based approaches. Omphaloceles with or without other anomalies, especially the subgroup called giant omphaloceles, may be associated with PAH caused by associated severe pulmonary hypoplasia.[537]

Diffuse interstitial lung diseases in infancy often stem from surfactant protein dysfunction disorders but also include other rare lung diseases, the most common of which include pulmonary growth abnormalities.[538] In a recently published series reviewing histopathology from infants and young children with diffuse lung disease from 11 centers, Deutsch and coworkers[538] divided the pulmonary growth abnormality group into prenatal and postnatal categories. Prenatal causes include anatomic or functional abnormalities that limit lung or thoracic growth in utero such as severe oligohydramnios, CDH, omphalocele, thoracic dystrophies and other skeletal disorders, neuromuscular disorders, certain chromosomal disorders, and cardiac disorders that limit pulmonary blood supply. Besides BPD and CDH, the most common associated conditions are CHD and chromosomal disorders.[538] It is well known that infants with Down syndrome often have lung hypoplasia, which increases the risk for PAH, which is accelerated in the setting of cardiac disease or intermittent hypoxia caused by OSA.[181,182] Beneficial responses to ERA or PDE5 inhibitor therapies have been reported in uncontrolled studies in subjects with Down syndrome.[181,539] The actual prevalence, natural history, and response to therapy of PAH in infants and young children with pulmonary growth abnormalities are unknown.

Because PVD can masquerade as diffuse lung disease,[540] screening for PAH in all infants and children with these diseases is clinically indicated. Furthermore, the presence of PAH in patients with interstitial lung disease is associated with a worse prognosis.[538] Echocardiography to estimate RV pressure and to visualize the pulmonary veins is indicated in most of these patients.

The association between end-stage lung disease associated with cystic fibrosis and PH has been recognized for decades.[541] Past reports suggest that the degree of PH is usually not severe and that PH has been most commonly reported in adults with end-stage lung disease.[542] However, PH may still contribute to decreased exercise tolerance and quality of life in the setting of advanced cystic fibrosis.[543,544] Patients at risk for PAH appear to be those with the lowest lung function, especially individuals with hypoxemia with or without hypercapnia. Stecenko et al[545] reported that a forced vital capacity of <35% of the predicted value was the most accurate spirometric predictor of a Pao_2 <55 mm Hg. Although most subjects with severe cystic fibrosis have relatively mild elevations of PVR at rest, exercise-induced elevation of PH may worsen exercise tolerance, which may improve with PH-specific therapy.[544] Controlled studies of PAH pharmacotherapy in patients with cystic fibrosis are lacking, but there are experimental and anecdotal data to support the use of either ERA therapy or PDE5 inhibitor therapy.[544]

There have been many case reports of OSA with PAH and cor pulmonale in the medical literature, most commonly associated with predisposing disease entities. However, studies of OSA in otherwise normal children with enlarged tonsils and adenoids estimate a 3% to 21% incidence of RVH by ECG or echocardiography, respectively.[546,547] Likewise, in otherwise healthy children with OSA diagnosed by polysomnography, 37% had decreased RV ejection fraction as measured by radionuclide ventriculography.[548] Despite these consequences of OSA, recent guidelines omit any reference to diagnostic testing for PAH in children with OSA. The 2002 American Academy of Pediatrics guideline notes that "cor pulmonale with heart failure in children with OSA…is now rare."[549] The recent American Academy of Otolaryngology clinical practice guideline makes no reference to the need for cardiac evaluation of children with OSA.[550] However, this may reflect the need for further studies to define the prevalence and impact of PH in this setting, especially in at-risk populations such as subjects with BPD, CDH, Down syndrome, CHD, and other disorders. It is recommended that echocardiography be performed in selected children with OSA awaiting elective surgery who are included in these at-risk conditions, have a past history of lung or heart disease, or have signs of RV dysfunction, systemic hypertension, or multiple hypoxemic episodes on polysomnography.[551]

Overall, PH is associated with diverse lung diseases in children, ranging from developmental disorders at birth or in early life to acquired disorders in later childhood. The incidence of PH in these disorders, except for ACD, has not been rigorously evaluated. The role of PAH pharmacotherapy in patients whose primary abnormality is lung disease remains speculative.

Although the value of PAH-targeted therapy is unproved, the association of PH with intrinsic lung disease confers a significant increase in morbidity and mortality. Thus, it is imperative that clinicians have a high degree of suspicion for the presence of PH in these entities. Patients with primary diagnoses such as scimitar syndrome, giant omphalocele, and surfactant protein dysfunction syndromes and individuals with pulmonary growth abnormalities should undergo formal evaluation for PAH with screening echocardiography.

Recommendations

1. **Children with chronic diffuse lung disease, especially those with advanced disease, should be evaluated for concomitant cardiovascular disease or PH by echocardiogram (*Class I; Level of Evidence B*).**
2. **Echocardiography is recommended to assess PH and RV function in patients with severe OSA (*Class I; Level of Evidence B*).**
3. **For exercise-limited patients with advanced lung disease and evidence of PAH, the following is recommended:**
   a. **A trial of PAH-targeted therapy is reasonable (*Class IIa; Level of Evidence C*).**

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b. Catheterization of the right side of the heart may be considered (*Class IIb; Level of Evidence B*).

13. Hypobaric Hypoxia and High Altitude–Related Illnesses

Ambient oxygen tension decreases with altitude, and the resulting airway hypoxia elicits hypoxic pulmonary vasoconstriction. If exposure to altitude is sustained, altitude can cause chronic PH, especially in genetically susceptible individuals. The magnitude of the effect of environmental hypoxia on the pulmonary vasculature depends on many factors, including the patient's age, genetic background, and the elevation to which he or she is exposed.[552,553] Populations who have lived at high altitude for millennia are relatively resistant to the adverse effects of high altitude, whereas lowland natives are more susceptible and retain this susceptibility for many generations. The rate of ascent to altitude is an additional determinant of whether altitude will cause acute symptomatic PH with pulmonary edema (HAPE). Gradual ascent to altitude improves tolerance of hypoxia and reduces the risk for HAPE. There is little evidence to guide therapy for high altitude–related PH in children. In the absence of RCTs, recommendations are based on anecdotal reports, retrospective review of clinical experience, expert judgment, or, in some cases, extrapolation of data obtained from adult subjects. Although PH is an essential feature of chronic mountain sickness (or Monge disease), children are seldom affected.[554] In contrast, HAPE and symptomatic high-altitude PH (SHAPH) affect infants and children as well as adults.

13.1. Symptomatic High-Altitude PH

Although originally described as pediatric high altitude heart disease or subacute infantile mountain sickness, an ad hoc committee of the International Society for Mountain Medicine[555] recommended that the term SHAPH most concisely and accurately describes this condition. SHAPH most commonly afflicts infants but also children, primarily offspring of Chinese of Han ancestry who have moved from low altitude to the Qinghai-Tibet Plateau. SHAPH most frequently occurs above 3000 m.[556] There are sporadic reports of SHAPH outside Tibet, including reports from La Paz, Bolivia,[557] and Leadville, CO.[558] Unlike patients with Monge disease, patients with SHAPH do not present with polycythemia. Presenting symptoms of SHAPH are consistent with congestive heart failure. Physical examination, ECG, and chest x-ray indicate RVH and RV dilation, PH, and congestive heart failure. Mortality has been reported at 4% to 15%.[556] Compared with age-matched control subjects, Doppler estimates of PAP are higher in infants with SHAPH (67±7 mm Hg) than in control subjects (34±4 mm Hg). MRI revealed that patients with SHAPH have thicker RV walls and reduced RV ejection fractions.[559] Postmortem examination confirmed RVH and dilation, dilation of the main PA, and medial hypertrophy with adventitial thickening of small arteries.[560]

For patients whose evaluation is consistent with SHAPH and whose PH resolves with therapy (see below), it is not clear that cardiac catheterization is required. When noninvasive evaluation is not consistent with SHAPH or when PH persists despite relocation to low altitude, cardiac catheterization may provide valuable information about comorbidities or predisposing factors. For infants who present with SHAPH in the first 6 months of life and are refractory to therapy, consideration should be given to lung biopsy, given the possibility of ACD or other developmental lung diseases. There are no RCTs to guide therapy for SHAPH. Practitioners experienced with SHAPH recommend prompt relocation to low altitude as definitive therapy.[555]

13.2. High-Altitude Pulmonary Edema

HAPE is an acute increase in PAP with normal LA pressure that is stimulated in susceptible individuals by exposure to hypoxia. HAPE results in pulmonary edema caused by transudation of protein-rich fluid from small pulmonary vessels into the airspaces.[561,562] Patients with a history of HAPE have greater hypoxic pulmonary vasoconstriction than normal subjects who have resting PH.[563,564] There is marked variability in individual susceptibility, and HAPE tends to recur in susceptible individuals, consistent with an unidentified genetic HAPE diathesis. In adults, HAPE occurs much more often in male than female individuals but has a roughly equal sex distribution in children. HAPE-susceptible subjects react to acute alveolar hypoxia and exercise with a greater increase in PAP than nonsusceptible individuals.[562–564] Children are at risk of HAPE, as reported in early studies.[561] Unlike SHPAH, which is rare, HAPE is common and afflicts people residing in or visiting the Rocky Mountains and other high-altitude resorts.[565–567] The are 2 types of HAPE: that which afflicts lowlanders who rapidly ascend to altitudes above 2500 m (although lower altitudes have been associated with HAPE[568]) and re-entry HAPE, which occurs in high-altitude residents who return to high altitude after sojourning (for as little as a day) to low altitude.[565] The more rapidly one gains altitude above 2500 m, the greater the susceptibility to HAPE is (see below). The incidence of HAPE with rapid ascent to 4559 m is 7% in mountaineers without previous HAPE but 62% in those with a prior episode.[569] HAPE is much less common at lower altitudes, with an estimated incidence among visitors at 2 Colorado ski areas at 2500 to 3000 m between ≈0.1% and 0.01%.[567]

HAPE is associated with viral illness in children[570] and multiple disorders, including absent left or right PA,[571] ASD, PDA, pulmonary vein stenosis, trisomy 21, BPD, and other diseases.[566,572] The onset of HAPE is usually 2 to 4 days after rapid ascent to altitude (or rapid ascent to a new, higher altitude). Presenting symptoms include cough, exertional dyspnea, and reduced exercise performance. Criteria for diagnosing HAPE in previously healthy children include rapid ascent to altitude above ≈2500 m, having ascended from altitudes >2500 m at a rate exceeding ≈300 m/d, and the above signs, symptoms, and x-ray findings. Other possible conditions (in children, most commonly pneumonia and asthma) must be considered. Because patients with HAPE typically improve rapidly (within minutes) with enriched inspired O_2, patients who do rapidly improve merit consideration for further investigation for other causes of PH.

Slow ascent is effective and is the first-line preventive measure. Recommendations for maximum rate of ascent >2500 m

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range from 300 to 600 m/d.[555,573] Some experts also recommend a rest day for every 600 to 1200 m gained. Avoidance of vigorous exertion before being well acclimatized and delaying further elevation gain if symptoms of HAPE appear are also helpful. There are no randomized trials of prevention or therapy for HAPE in children, and all recommendations are based on adult trials. In a placebo-controlled RCT of prophylactic use of extended-release nifedipine in 21 adults with a history of HAPE who ascended rapidly to 4559 m, nifedipine reduced the incidence of HAPE from 7 of 11 (placebo subjects) to 1 of 10 (treated subjects).[574] For patients with a history of HAPE, nifedipine is recommended; it should be started with the ascent and continued for 3 to 4 days after arrival at the terminal altitude. Alternatives to nifedipine include PDE5 inhibitors and dexamethasone. A double-blind, placebo-controlled RCT of tadalafil and dexamethasone in adults with a history of HAPE suggested that that each of these medications may reduce the incidence of HAPE.[575] However, tadalafil was associated with severe acute mountain sickness in 2 subjects, as has been reported with sildenafil.[576] Sildenafil has been suggested for HAPE prophylaxis in adults.[577] Immediate descent to lower altitude and administration of supplemental O_2 are the primary therapies for adults and children with HAPE.

13.3. High Altitude and CHD

In children with CHD, including large VSD[107] and congenital mitral stenosis,[578] exposure to even modest altitude increases PVR. The incidence of PH may be higher in children with ASD who reside at 1300 to 1600 m[579,580] compared with those at sea level. With Fontan palliation, PVR greatly affects hemodynamic status, suggesting that these patients might be vulnerable to complications of hypoxia at high altitude.[581] However, some reports suggest that Fontan survival is roughly the same at moderate altitude (1370–1600 m) and sea level.[582,583] Exercise capacity, however, is reduced in Fontan patients at moderate or high altitude compared with sea level.[583–585] Insufficient information exists to determine whether residence at high altitude should change the indications (relative to those used at sea level) for or timing of repair of intracardiac shunting lesions. Because PVR may be considerably higher at high altitude, some patients considered inoperable (ie, whose PVR is too high to permit closure of a shunting lesion) at high altitude or after recently moving to low from high altitude may in fact be suitable for operation after a period of residence at low altitude.

For patients with Fontan palliation residing at high altitude, an important question is whether pulmonary vasodilators, especially those shown to reduce hypoxic pulmonary vasoconstriction (nifedipine and sildenafil), might have a favorable impact. A retrospective review of Fontan patients living at 1610 m found that long-term sildenafil therapy increased arterial O_2 saturation, reduced edema and pleural effusions, and decreased PVR.[586] Interpretation of these data is complicated by concomitant interventions (eg, periods of residence at sea level, PA angioplasty, collateral occlusion) and often a lengthy interval between initiation of sildenafil and reported outcome. A prospective, randomized exercise study reported that sildenafil increases maximum O_2 consumption in Fontan patients at sea level.[365] Several case reports indicate beneficial effects of sildenafil in Fontan patients at low altitude,[410,587,588] but most of the patients underwent other interventions during the study period. A double-blind, placebo-controlled, crossover RCT of sildenafil for 6 weeks on exercise performance at sea level found small improvements in respiratory rate and minute ventilation at peak exercise.[366] Overall, available information suggests that sildenafil may be helpful in reducing morbidity and increasing exercise performance in Fontan patients at high or low altitude.

Recommendations

1. **Patients with symptomatic high altitude–related PH may be encouraged to move to low altitude (*Class IIb; Level of Evidence C*).**
2. **CCB therapy (with amlodipine or nifedipine) may be reasonable for HAPE prophylaxis in children with a history of HAPE (*Class IIb; Level of Evidence C*).**
3. **Therapy for symptomatic HAPE should include supplemental oxygen therapy and consideration of immediate descent (*Class I; Level of Evidence B*).**
4. **Children with HAPE should undergo evaluation to rule out abnormalities of pulmonary arteries or pulmonary veins, lung disease, or abnormal control of breathing (*Class I; Level of Evidence B*).**

14. Systemic Disease

14.1. Portopulmonary Hypertension

When PH accompanies portal hypertension, the resulting syndrome is called PPHTN. Among patients with cirrhosis, 0.61% had findings of PVD consistent with PH.[589] Recent cohort studies demonstrate that 5% to 6% of patients presenting for evaluation for liver transplantation have PH.[590] Although the association between PH and liver disease was initially reported in 1951,[591] the underlying cause of the association remains unknown.

Relatively recently, specific criteria have been adopted in adult patients for the diagnosis of PPHTN. Current diagnostic criteria for PPHTN mirror the criteria for other types of PH.[592] In the presence of either hepatopulmonary syndrome or PPHTN, the risk of death for patients with end-stage liver disease increases significantly.[593] The pulmonary vascular disorders associated with both hepatopulmonary syndrome and PPHTN can resolve after liver transplantation.[594] PPHTN is most commonly diagnosed in patients with end-stage liver disease and occurs in the context of biliary atresia, portal vein thrombosis, and Budd-Chiari syndrome. Although PPHTN occurs most frequently in the fourth and fifth decades of life, it clearly presents in children as well.

In addition to portal hypertension, risk factors for the development of PPHTN include female sex, positive serological markers for autoimmune disease (antinuclear antibodies), and the diagnosis of autoimmune hepatitis or chronic hepatitis C infection.[595,596] Data from the French Registry of PAH in adult patients indicate overall survival rates at 1, 3, and 5 years of 88%, 75%, and 68%, respectively.[597] In the absence of treatment, outcomes are significantly worse, with a median survival of 15 months and 5-year survival rate of 14%.[592]

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Survival is indirectly correlated with the severity of cirrhosis and degree of compromise of RV function.

PPHTN has been reported in children with portal hypertension and is often due to cirrhosis or portal vein pathology.[598] The incidence of these complications in children is unknown.[599] In children with PPHTN, plexogenic pulmonary arteriopathy is associated with raised mPAP but with a normal wedge capillary pressure.[600] Echocardiograms are recommended for the evaluation of children with PPHTN or hepatopulmonary syndrome in the setting of hypoxemia and cardiopulmonary signs and symptoms. Moreover, right-sided heart catheterization is required for more accurate hemodynamic assessment and achieving a definitive diagnosis of PPHTN and is essential in evaluating children for transplantation. Children with PPHTN should not be anticoagulated because of the increased risk of severe hemorrhage.

14.2. Chronic Hemolytic Anemia

PH diagnosed by Doppler echocardiography is relatively common in adults with SCD and is strongly associated with increased mortality.[601] According to cardiac catheterization studies, the prevalence of PH in adults with SCD is 6% to 11%.[602–604] Importantly, an increased *tricuspid regurgitant jet velocity* (TRJV) by echocardiography, elevated serum NT-proBNP levels, and PH diagnosed by cardiac catheterization are independent risk factors for mortality. Adults with SCD who have TRJV ≥2.5 m/s have a 10-fold greater risk for death than those with lower TRJV.[601]

Although children as young as 3 years of age with SCD have been diagnosed with PH, the incidence increases in the second decade, and mortality in pediatrics is rare.[605] Elevated TRJV has been reported in 10% to 20% of children with SCD, but its impact on mortality is less clear than in adults.[606,607] Children with high TRJV did not differ from control subjects in episodes of acute chest syndrome, hospitalization, or stroke.[608] In children >8 years of age, TRJV may reflect morbidity risk rather than mortality but also provides comparative data for follow-up. Children with elevated TRJV and severe hemolytic anemia were at highest risk for decreased 6MWD after 2 years of follow-up.[606] Serum NT-proBNP is reasonable for screening for PH if Doppler echocardiography is not available or is unclear. Children with early findings of PH should be evaluated for chronic or intermittent hypoxia, pulmonary function testing, sleep studies, and perhaps ventilation/perfusion scan for risks for thrombi. Additional noninvasive testing to determine the severity of PH in pediatric SCD has included CT scans, BNP and NT-proBNP, and cardiopulmonary stress testing. However, there currently are no definitive data to recommend these tests over catheterization of the right side of the heart.

Few reports on the diagnosis of PH in children with SCD have included cardiac catheterization. Evaluation of TRJV in children with SCD has greater interobserver variance compared with adult studies, suggesting that diagnostic error may be increased in children.[609] Although TRJV ≥2.5 m/s is abnormal and values ≥3.0 m/s suggest moderate to severe PH, correlations between TRJV and PVR as measured during cardiac catheterization may be poor in pediatric patients with SCD.[610]

Importantly, increased TRJV does not necessarily imply the presence of elevated PVR. In patients with SCD, TRJV can be increased as a result of several factors, and echocardiography is not sufficient to distinguish precapillary from postcapillary PH. This distinction is critical in determining whether a patient with PH and SCD may potentially benefit from PAH-specific drug therapy. For example, PH criteria for patients with SCD include mPAP ≥25 mm Hg with mean PA wedge pressure or LV end-diastolic pressure <15 mm Hg plus increased PVR. However, high cardiac output resulting from anemia and reduced blood viscosity may reflect a lower PVR despite a high TRJV. In addition, PH in children with SCD may be due to postcapillary factors, including high left-sided pressures, and evaluation of LV filling pressure is not available by echocardiography or noninvasive studies. In addition to high mPAP, SCD patients with postcapillary PH have an increased PA wedge pressure or LV end-diastolic pressure >15 mm Hg. Pulmonary edema and hypoxemia can occur with escalation of vasodilator treatment if LV dysfunction is underestimated. As a result, cardiac catheterization is needed to most accurately characterize the nature of PH in SCD, which has therapeutic implications for the use of PAH-targeted drug therapies.

Therapy for SCD-associated pediatric PH has not been fully evaluated. On the basis of adult data for high mortality risk, for children with SCD and PH based on high TRJV by echocardiogram (>2.5 m/s), high NT-proBNP >160 pg/mL, or mPAP >25 mm Hg by cardiac catheterization, we generally recommend more aggressive treatment with SCD therapies, including hydroxyurea and long-term transfusion therapy.[611] However, there is a suggestion that hydroxyurea, a current therapy that decreases hemolysis, may be associated with an increased risk of PH.[612] For patients with SCD who have PH that is confirmed by cardiac catheterization, we recommend against PAH-targeted therapy except for those with high PVR and normal pulmonary capillary wedge pressure. In these patients, we recommend a trial of either a PGI_2 analog or an ERA. Preference for these categories of drugs over PDE5 inhibitors is based on the observation of an increased risk for pain crisis and hospitalization in SCD patients with PH.[613] For those with catheterization-confirmed evidence of PH and high PA wedge pressure, we recommend against the use of PAH-specific therapy.

14.3. Autoimmune Disease

The term autoimmune disease covers a broad array of disease entities, most of which are not associated with PAH. Those diseases most likely associated with PAH are in the subcategory of CTD. In adult populations, ≈20% of patients have CTD, most commonly scleroderma and systemic lupus erythematosus.[614] The incidence of CTD in general and of CTD associated with PAH is much lower in pediatric series. In a recently published Dutch series, only 3 of 154 pediatric patients with PAH had associated CTD.[615]

Juvenile-onset scleroderma is a well-recognized form of scleroderma. In 2 large series of children and adolescents with juvenile-onset scleroderma, the incidence of PAH before 21 years of age was <10%.[106,616] However, when PAH is present in juvenile scleroderma, it can be fatal. PAH is much less

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common in systemic lupus erythematosus than in scleroderma.[617] Although the incidence of PAH in systemic lupus erythematosus has been reported to be up to 10% in adult populations, it appears to be significantly less common in pediatric patients with systemic lupus erythematosus.[618] PAH may also be associated with other less common rheumatological disorders. A recent report of 3 pediatric patients with atypical CTD suggests that PH can precede the subsequent development of joint disease or positive serology.[619] Because of the low incidence of CTD-associated PAH, there is little information on the safety and efficacy of PAH pharmacotherapy in PAH associated with CTD. It seems appropriate to extend the generally positive experience of PAH pharmacotherapy in scleroderma in adults[620] to a tailored, individualized approach to childhood CTD. The relative importance of anti-inflammatory therapies to modulate the underlying autoimmune process versus PAH therapy requires further study.

Overall, PAH is an uncommon complication of CTD in childhood, but strong consideration for screening echocardiography is appropriate because of the high associated morbidity and mortality. PAH has also been diagnosed rarely in children with mixed CTD and Sjögren syndrome. PAH is even less common in juvenile rheumatoid arthritis. In all children with newly diagnosed PAH, screening testing, especially an antinuclear antibody profile, should be considered. It may be appropriate to repeat testing 2 years after the initial diagnosis or in the clinical context of any symptom suggestive of CTD.

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14.4. Infectious Diseases

The connection between infectious agents and PAH is most clearly delineated in association with HIV and schistosomiasis, each of which is recognized in the most recent iteration of the WHO classification of PH.[5] The incidence of PAH in patients with HIV infection has been estimated at 0.5%, an incidence that has not been altered by the availability of highly active retroviral therapy.[621] HIV-infected alveolar macrophages produce specific proteins that cause angioproliferation in the pulmonary vascular bed.[622] There are case reports of PAH in HIV-infected individuals, mostly adults. All forms of PAH pharmacotherapy have been used in HIV-infected patients, often with short-term benefits.[623] Mortality is largely related to the progression of PAH as opposed to the progression of HIV infection. Inconsistent evidence suggests that human herpesvirus-8 may cause PAH, either in conjunction with Castleman disease[623] or in IPAH.[624] The link between human herpesvirus-8 and PAH, however, remains speculative and a subject of research. Routine testing for human herpesvirus-8 in pediatric patients with PAH is not indicated.

Schistosomiasis is endemic in Africa, Southeast Asia, China, and some parts of Brazil. Only a small fraction (5%–10%) of infected patients develop hepatosplenic disease, which is the most morbid clinical form of schistosomiasis.[625] Of that group, 7% to 10% develop PAH.[626,627] From published studies, the vast majority of diagnosed patients have been adults. By the time that clinical manifestations of PAH appear, chronic fibrotic changes in and around the pulmonary vascular bed may bode for poor prognosis,[625] but there is recent evidence to support the use of PAH pharmacotherapy.

In summary, both HIV and schistosomiasis are potentially preventable and treatable diseases that, in certain circumstances, can lead to PAH. There are limited data on the prevalence of PAH in pediatric populations with these infections. There are preliminary data in adults that PAH pharmacotherapy may have a role in modifying disease progression.

14.5. Other Disease States

Oncological, metabolic, and endocrine diseases and chronic renal failure with dialysis have been associated with a low prevalence of PH in adults. Although published data are limited, small case series and clinical experience in most PH programs speak to a growing recognition of PH in these diverse settings.

Recommendations

1. **Early evaluation for PH, including a Doppler echocardiogram, is reasonable for children with hemolytic hemoglobinopathies or hepatic, renal, or metabolic diseases who develop cardiorespiratory symptoms (*Class IIa; Level of Evidence C*).**
2. **In children with chronic hepatic disease, an echocardiogram should be performed to rule out PPHTN and pulmonary arteriovenous shunt before listing for liver transplantation (*Class I; Level of Evidence B*).**
3. **It is reasonable for children with SCD to undergo an echocardiogram to screen for PH and associated cardiac problems by 8 years of age or earlier in patients with frequent cardiorespiratory symptoms (*Class IIa; Level of Evidence C*).**
4. **The following are recommended for children with SCD who have evidence of PH by echocardiogram:**
   a. **These children should undergo further cardiopulmonary evaluation, including pulmonary function testing, polysomnography, assessments of oxygenation, and evaluation for thromboembolic disease (*Class I; Level of Evidence C*).**
   b. **These children should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (*Class I; Level of Evidence C*).**
5. **BNP and NT-proBNP measurements can be useful in screening for PH in patients with SCD (*Class IIa; Level of Evidence C*).**
6. **With the diagnosis of PH in children with SCD, optimization of SCD-related therapies (eg, blood transfusions, hydroxyurea, iron chelation, and supplemental oxygen) is recommended (*Class I; Level of Evidence C*).**
7. **PAH-targeted therapy should not be used empirically in SCD-associated PH because of potential adverse effects (*Class III; Level of Evidence C*).**
8. **PAH-targeted therapy may be considered in patients with SCD in whom there is confirmation of PH with marked elevation of PVR without an elevated pulmonary capillary wedge pressure by cardiac catheterization (*Class IIb; Level of Evidence C*).**
9. **A trial of a PGI_2 agonist or an ERA is preferred over PDE5 inhibitors in patients with markedly elevated PVR and SCD (*Class IIa; Level of Evidence B*).**

15. Outpatient Care of Children With PH

Many aspects of care that affect the long-term course of children with PH involve clinical issues beyond PAH-specific diagnostics and therapies alone. As reflected by the extensive list of diverse diseases and comorbidities associated with pediatric PH (Table 6), improving outcomes of the child with PH requires establishing experienced, knowledgeable, and multidisciplinary pediatric PH programs. Teams of pediatric subspecialists from pulmonology, cardiology, neonatology, critical care, anesthesiology, and other areas have much to offer to improve the care of children with PH. The PH team must also include well-trained and experienced nurses and nurse practitioners who help provide short- and long-term care and ensure strong continuity of care. These healthcare professionals are essential for optimizing patient care; family teaching; handling many questions about disease course, exacerbations, and intercurrent illnesses; and patient and family support. Patients with PH require around-the-clock availability of a PH team member because a routine illness may pose life-threatening risk to the patient.

The need to develop pediatric PH programs is based on several other factors, including the rapidly changing availability of new PAH-specific drug treatments and novel diagnostic and therapeutic technologies. Well-coordinated short- and long-term continuity of care for children with PH and their families is needed to optimize outcomes. Although the rationale for developing pediatric PH programs and enhancing their impact through the development of interactive networks has been described,[3] studies that specifically define the essential elements for successful pediatric PH programs and how to best optimize care remain lacking. A critical aspect includes the successful coordination of inpatient and outpatient care. Because more children are surviving to adulthood, strategies for successfully transitioning pediatric patients to adult care are also mandatory.

Models of defining optimal care centers through established networks have been provided by pioneering work of the Cystic Fibrosis Foundation, the Childhood Oncology Group, and others that have had a huge impact on enhancing care and outcomes of children with rare diseases. In each case, establishing standardized approaches, developing extensive databases and registries, encouraging interactions among programs, and enhancing research support have standardized care, increased survival, and improved the quality of life for many children and their families. It is likely that similar approaches may also enhance outcomes for children with PH.

Many aspects of care for children with PH include recommendations that are based on extensive experience and studies of children with chronic cardiac and respiratory disorders, including CHD, BPD, and asthma. In these settings, frequent outpatient visits allow close monitoring of changes in disease course and enhance communication with families and care providers.[628,629] Because respiratory viral and bacterial infections are common throughout childhood and adversely affect outcomes of children with PH, we make similar recommendations for the use of respiratory syncytial virus, influenza, and pneumococcal vaccines as defined in these other settings.[629–631] In addition, involvement of an experienced PH team during even routine surgical and dental procedures can reduce complications related to anesthesia in children with PH.[78,79,632] Recommendations concerning the potential harm of pregnancy in young women with PH,[633] caution with intense exercise,[134,634] and the availability and use of supplemental oxygen for airplane travel,[635] as well as the growing awareness that family issues are especially critical for childhood disease,[636] are also highlighted.

Recommendations

1. **Children with PH should be evaluated and treated in comprehensive, multidisciplinary clinics at specialized pediatric centers (*Class I; Level of Evidence C*).**
2. **Outpatient follow-up visits at 3- to 6-month intervals are reasonable, with more frequent visits for patients with advanced disease or after initiation or changes in therapy (*Class IIa; Level of Evidence B*).**
3. **The following preventive care measures for health maintenance are recommended for pediatric patients with PH:**
   - **Respiratory syncytial virus prophylaxis (if eligible)**
   - **Influenza and pneumococcal vaccinations**
   - **Rigorous monitoring of growth parameters**
   - **Prompt recognition and treatment of infectious respiratory illnesses**
   - **Antibiotic prophylaxis for the prevention of subacute bacterial endocarditis in cyanotic patients and those with indwelling central lines (*Class I; Level of Evidence C*).**
4. **Careful preoperative planning, consultation with cardiac anesthesia, and plans for appropriate postprocedural monitoring are recommended for pediatric patients with PH undergoing surgery or other interventions (*Class I; Level of Evidence C*).**
5. **Elective surgery for patients with pediatric PH should be performed at hospitals with expertise in PH and in consultation with the pediatric PH service and anesthesiologists with experience in the perioperative management of children with PH (*Class I; Level of Evidence C*).**
6. **Because of the significant maternal and fetal mortality associated with pregnancy in patients with PH, it is recommended that female adolescents with PH be provided age-appropriate counseling about pregnancy risks and options for contraception (*Class I; Level of Evidence C*).**
7. **Because of the risks of syncope or sudden death with exertion, it is recommended that a thorough evaluation, including CPET and treatment, be performed before the patient engages in athletic (symptom-limited) activities (*Class I; Level of Evidence C*).**
8. **Pediatric patients with severe PH (WHO functional class III or IV) or a recent history of syncope should not participate in competitive sports (*Class III; Level of Evidence C*).**
9. **During exercise, it is recommended that pediatric patients with PH engage in light to moderate aerobic activity, avoid strenuous and isometric exertion, remain well hydrated, and be allowed to self-limit as required (*Class I; Level of Evidence C*).**

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10. **During airplane travel, supplemental oxygen use is reasonable in pediatric patients with PH (*Class IIa; Level of Evidence B*).**
11. **Given the impact of childhood PAH on the entire family, children, siblings, and caregivers should be assessed for psychosocial stress and be readily provided support and referral as needed (*Class I; Level of Evidence C*).**

16. Conclusions

Despite many advances in our understanding of the pathobiology and treatment of PHVD, care guidelines have not previously been developed for specific use in children. The purpose of this document is to provide a general overview of PVD in neonates, infants, and children and recommendations for the assessment and treatment of children with PH. As noted, many gaps remain in our knowledge of the developing lung circulation and its response to injury, unique features of PH in children, and optimal clinical evaluations and treatment strategies. This document is intended to provide a foundation for future work directed toward additional discoveries of basic and clinical aspects of disease that will ultimately improve the quality of life and long-term outcomes of children with PVD in diverse settings.

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*Modest.

†Significant.

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