EXECUTIVE SUMMARY OF AMERICAN THORACIC SOCIETY DOCUMENT

Executive Summary of the American Heart Association and American Thoracic Society Joint Guidelines for Pediatric Pulmonary Hypertension

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Abstract

Although pulmonary hypertension (PH) contributes significantly to poor outcomes in diverse pediatric diseases, approaches toward the care of children with PH 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 committee of experienced clinicians was formed to systematically identify, synthesize, and appraise relevant evidence and then to formulate evidence-based recommendations regarding the diagnosis and management of pediatric PH. This brief report is an executive summary of the officially approved guidelines developed by the committee, highlighting a few key recommendations regarding the care of children with PH. Guidelines and the rationale for grading the strength of each recommendation are included in the online supplement.

Introduction and Rationale

Pulmonary hypertension (PH) and related pulmonary vascular diseases (PVD) contribute significantly to poor outcomes in diverse pulmonary, cardiac, and systemic disorders in children (1–5). Despite advances in our understanding of its pathobiology and the growing availability of drug therapies, PH-related morbidity and mortality remain high. More recently, PH-related hospitalizations and resource use for the care of children with PVD have increased, likely reflecting growing recognition of the relevance of PH in diverse clinical settings or perhaps an actual increase in the incidence of disease (4). Although similarities exist regarding disease etiology and pathophysiology of some forms of pediatric and adult PH, many cardiopulmonary and systemic diseases associated with PH are unique to neonates, infants, and children (2, 3, 5).

Most importantly, the developmental biology of the growing lung and its circulation play a key role in disease pathogenesis, pathophysiology, and outcomes. Vascular injury during susceptible periods of lung growth and adaptation can have longstanding effects throughout childhood and may impact distal lung airspace structure as well (6). The most striking examples include the important impact of PVD after premature birth, the contribution of PVD to poor outcomes in many developmental lung diseases, the association of PVD with genetic syndromes (especially Down syndrome), and other factors that reflect both prenatal and postnatal influences that may act through epigenetic mechanisms (7, 8). Along with hemodynamic changes during the transition at birth, normal maturation of the lung circulation also plays a critical role during lung

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*A complete list of members may be found before the beginning of the References.

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organogenesis and formation of the distal airspace through angiocrine signaling, and disruption of endothelial function can impair lung structure in diverse neonatal diseases (9, 10). In addition, perinatal factors may increase the risk for the late development of PH in adulthood, suggesting that an important maturational window may exist during which early identification of susceptibility factors may permit interventions that can reduce the incidence or severity of PAH (11). Pediatric PH is also distinct from adult disease in that there are striking maturational differences in responsiveness to PAH-specific therapies related to poorly understood, age-related alteration of drug pharmacodynamics and pharmacokinetics and, perhaps, a greater risk for late adverse effects (12–15).

Pediatric PH has been understudied, and relatively little is known about basic disease mechanisms, natural history, long-term outcomes, age-appropriate clinical endpoints, optimal therapeutic strategies, and unique adverse effects of drugs in the developing infant (3). A persistent barrier toward enhancing the clinical care and research in children includes the lack of clear parameters for assessing functional class in infants and young children, especially in the setting of developmental disabilities. Studies of pediatric PH are often complicated by the marked heterogeneity of associated conditions and comorbidities, the relatively small number of patients at each center, an overreliance on anecdotal experience, and/or unjustified extrapolation from adult-based PH studies (3, 5). Integrating the management of critical comorbidities that impact long-term outcomes in specific pediatric diseases with PH, such as bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH), and developmental lung diseases, with the treatment of PH itself is difficult and further complicates developing useful treatment algorithms.

Moreover, there is uncertainty how to best monitor disease progression or response to therapy in pediatric PH. Whether early recognition or the application of preventive therapeutic strategies in children can minimize disease severity during adulthood remains unproven. Thus, more research is required to improve our understanding of the natural history, fundamental disease mechanisms, and optimal treatment of many pediatric PH disorders.

Limitations to performing adequate studies of the pediatric population include the many associated conditions that fragment the classification of pediatric PH, challenges in obtaining informed consent, the relatively small numbers of patients with PAH at each center, the scarcity of multidisciplinary pediatric PH programs, and suboptimal communication between PH scientists and PH clinicians. There is clearly a need to better define the natural history of pediatric PAH, to develop new strategies to identify patients at risk for development of PH, and to develop and test novel biomarkers, drugs, and devices to diagnose, monitor, and treat children with PH.

With collaborations of the American Heart Association (AHA) and American Thoracic Society (ATS), a committee of experienced clinicians was formed to systematically identify, synthesize, and appraise relevant evidence and then to formulate evidence-based recommendations regarding the diagnosis and management of pediatric PH, which were published in the AHA-sponsored journal, *Circulation* (5). This brief report provides an executive summary of the officially approved guidelines developed by the committee, highlighting a few key recommendations regarding the care of children with PH. Guidelines and the rationale for grading the strength of each recommendation are included in the online supplement.

General Approach and Methods

A committee of experienced PH clinicians was established to create clinical practice guidelines for the care of children with PH under the auspices of the AHA and ATS. The purpose of the task force was to develop recommendations that answer high-priority clinical questions on the basis of comprehensive evidence syntheses. The task force was multidisciplinary by design, including pediatric pulmonologists, pediatric and adult cardiologists, pediatric intensivists, neonatologists, and translational scientists. Members were selected from recommendations of the Pediatric Assembly of the ATS and the Practice Guidelines Committee of the AHA. All members were thoroughly vetted by the AHA and ATS to avoid actual, potential, or perceived conflicts of interests and relationships with industry (*see* Supplemental Table 1 in Reference 5).

Subgroups were formed to focus on specific areas within each of the key topics. Medical librarians performed comprehensive literature searches and then, for each question, the subgroups selected relevant studies, summarized the benefits and harms of the intervention, rated the quality of evidence, and formulated preliminary recommendations. This information was subsequently presented to the full task force, after which there was discussion. The task force frequently modified the recommendations, and then the strength of the recommendation was determined. The AHA and ATS use different approaches to rate the quality of evidence and strength of the recommendation; for these guidelines, the AHA approach was used (*see* Supplement Table 2 in Reference 5). In the AHA approach, the Class of Recommendation is an estimate of the magnitude of the treatment effect, with consideration given to risks versus benefits. A Class I designation indicates that the benefits far exceed the risks, a Class II designation indicates that the benefits exceed or are equal to the risks, and a Class III designation indicates that the risk exceed the benefits. The Level of Evidence (LOE) is an estimate of the certainty of the estimated treatment effect. An LOE A rating conveys that the data were derived from multiple randomized clinical trials (RCTs) or metaanalyses, an LOE B rating indicates that data were derived from a single RCT or nonrandomized studies, and an LOE C rating indicates that inadequate data are available and recommendations are based on expert consensus and clinical experience.

While recognizing the lack of extensive published studies in children, especially the paucity of multicenter, randomized, placebo-controlled trials, the task force endeavored to develop practical guidelines that reflected the current state of the art. These guidelines were intended to assist health care providers in clinical decision making by describing generally acceptable approaches to the diagnosis and management of children with PH. It is acknowledged that in many cases recommendations are based on the consensus of nonsystemic clinical observations (i.e., expert opinion [LOE C]), rather than the results of multiple RCTs

(LOE A). Although the Guidelines attempt to define practices that meet the needs of most patients in most circumstances, 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 and the local medical and surgical expertise. As a result, there are likely clinical settings in which decisions that differ from these guidelines are 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.

Selected Recommendations

The following summary presents only selected examples from a comprehensive set of recommendations that were published as a complete report of the AHA/ATS Joint Guidelines for Pediatric Pulmonary Hypertension (5). A complete list and discussion of factors that contributed to the scoring of strength of the recommendations is presented in the online supplement to this Executive Summary.

Diagnostics, Assessments, and Monitoring

Recommendation 1: At the time of initial PH diagnosis, a comprehensive history and physical examination in combination with diagnostic testing for assessment of PH etiology/classification and formal assessment of cardiac function should be performed before the initiation of therapy at an experienced center (I, B). Due to disease complexity and the importance of clinical experience in performing PH-specific diagnostic procedures and selecting therapeutic strategies, the Committee recommends that the evaluation and care for pediatric patients with PH should be provided or at least comanaged at specialty PH centers. Initial evaluations should be comprehensive and offer the expertise from multidisciplinary medical subspecialists and members of the care team, including PH nurses and nurse practitioners, social workers, psychologists, physiotherapists, and other team members. Routine follow-up visits should be performed at 3- to 6-month intervals at a minimum, with more frequent visits for patients with advanced disease or poor responsiveness to therapy or after changes in therapy. Subjects who are comanaged with their primary physicians should be seen at least biannually or in consultation with PH specialty centers.

Recommendation 2: Cardiac catheterization is recommended before initiation of PAH-targeted therapy (I, B). Exceptions may include critically ill patients requiring immediate initiation of empirical therapy (I, B). Serial cardiac catheterizations with acute vasoreactivity testing are recommended during follow-up to assess prognosis and potential changes in therapy (I, B). Intervals for repeat catheterizations should be based on clinical judgment but include worsening clinical course or failure to improve during treatment (I, B). General goals for cardiac catheterization in children with PH are to: (*1*) confirm the diagnosis and PH severity, (*2*) measure the response to pulmonary vasodilators (acute vasoreactivity testing [AVT]) before starting drug therapy, (*3*) evaluate the need for changes in therapy, (*4*) exclude other factors contributing to disease, (*5*) assess operability in patients with CHD with systemic to pulmonary artery shunts, and (*6*) assist in the determination of suitability for heart or heart-lung transplantation. Catheterization should generally be performed at diagnosis before initiation of PAH-specific drug therapy. Exceptions may include critically ill patients requiring immediate initiation of advanced therapies or at centers without sufficient experience in performing such studies in children with PH. Procedures should be performed by pediatric catheterization teams experienced in PH to reduce related morbidity or mortality and to improve the quality of comprehensive studies. This recommendation places a high value achieving a correct definitive diagnosis and the initiation of beneficial therapy and a lower value on the risks of the procedures.

Recommendation 3: Cardiac catheterization should include AVT unless there is a specific contraindication (I, A). The minimal hemodynamic change that defines a positive response to AVT for children should be considered as a greater than or equal to 20% fall in pulmonary artery pressure and pulmonary vascular resistance/systemic vascular resistance without a decrease in cardiac output (I, B). The Committee suggests that catheterization studies should include AVT, especially in children with CHD, to assess whether the pulmonary vascular resistance (PVR) will decrease sufficiently for surgical repair to be undertaken in borderline cases. In general, positive AVT for borderline cases with post tricuspid shunts is defined as decreases in PVR index (PVRI) to less than 6 to 8 Wood units (WU) $\cdot$ m^2 or PVR/systemic vascular resistance (SVR) less than 0.3. However, AVT is only one measure used to define operability, and the whole clinical setting, such as the age of the patient and the type of lesion, need to be taken into consideration. Vasodilators used for AVT include inhaled nitric oxide (iNO, 20–80 ppm), 100% oxygen, inhaled or intravenous prostacyclin analogs, or intravenous adenosine. Temporary balloon occlusion of a patent ductus arteriosus (PDA), atrial septal defect, or, less often, ventricular septal defect may be undertaken to assess whether permanent occlusion would be beneficial or if there is a potential need for PAH-specific drug therapy. A decrease in pulmonary artery pressure (PAP) with temporary occlusion may indicate suitability for permanent shunt occlusion. This recommendation places a high value on avoiding the downsides of inappropriate drug selection for therapy and high-risk surgical intervention and places a lower value on the potential complications of cardiac catheterization when performed at experienced centers.

Genetics

Recommendation 1: Genetic testing with counseling can be useful for children with idiopathic PAH or in families with heritable PAH to allow for definition of etiology and identification of family members at risk and to inform family planning (IIa, C). Currently, many PAH experts do not routinely use genetic test results to guide management of the patient with PAH. This recommendation for genetic testing places high value on the duty of physicians to inform patients that PAH may affect other family members and a lower value on the cost and availability of such tests or the potential adverse psychological impact of positive test results; however, such testing must be accompanied by extensive genetic counseling.

Recommendation 2: Genetic testing of first-degree relatives of patients with monogenic forms of heritable PAH is

indicated for risk stratification (I, B), and it is reasonable to screen asymptomatic carriers with serial echocardiograms or other noninvasive studies (IIa, B). Genetic testing can be offered to any subject with a family history of PAH or idiopathic PAH (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. Genetic counseling should be performed before genetic testing for PAH to address complex concerns related to incomplete penetrance of mutations, the burden of surveillance for genetically at-risk family members, reproductive questions, the risk of genetic discrimination, and potential psychosocial issues of guilt and blame that can accompany genetically based diseases. Families should be referred to a genetic counselor with PAH experience. These recommendations place high value on the duty of physicians to inform patients and their families that PAH may affect other family members and a lower value on the potential psychological impact of positive test results, as the latter can be mitigated via counseling. These recommendations also place a high value on the early initiation of therapy and a lower value on the potential psychological impact, harms, burdens, and costs of the diagnostic evaluation.

Persistent PH of the Newborn

Recommendation 1: iNO is indicated to reduce the need for extracorporeal membrane oxygenation support in term and near-term infants with persistent PH of the newborn or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (I, A). Persistent PH of the newborn (PPHN) represents the failure to achieve and sustain the normal drop in PVR and increase in pulmonary blood flow and oxygenation required for neonatal adaptation. Timely recognition and therapy are important, because PPHN is associated with high rates of neonatal mortality and morbidity, including significant neurodevelopmental sequelae. iNO acutely improves oxygenation and decreases the need for extracorporeal membrane oxygenation (ECMO) support in newborns with PPHN and an oxygenation index greater than 25. iNO is Food and Drug Administration approved as specific pulmonary vasodilator therapy for PPHN in near-term and term infants, and these recommendations have the strongest level of support on the basis of evidence for efficacy and safety of iNO for PPHN from three multicenter randomized controlled trials, several other clinical studies, and extensive experience. The recommendations put a lesser value on the cost of this therapy, as iNO often obviates the need for ECMO, which is itself an expensive and more invasive therapy with severe adverse effects.

Recommendation 2: iNO can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (IIa, B). Multiple case series have shown that iNO therapy improves oxygenation and pulmonary hemodynamics in preterm infants with severe hypoxemia due to PPHN physiology, as has been observed in randomized trials for PPHN in near-term and term newborns. In preterm infants with PPHN physiology and either a large PDA or myocardial dysfunction, iNO therapy may cause pulmonary edema. The use of iNO for preterm infants with severe hypoxemic respiratory failure and PPHN is distinct from its potential role for the prevention of BPD, for which iNO is currently not recommended. Extensive multicenter trial experience for the prevention of BPD, however, provides clear information on the safety of iNO in preterm infants, as reflected by the lack of an increase in adverse events. This recommendation places a high value on offering a safe therapy for life-threatening PH over the lack of randomized clinical data showing efficacy for this use.

CDH

Recommendation 1: iNO therapy can be used to improve oxygenation in infants with CDH and severe PH but should be used cautiously in subjects with suspected left ventricular dysfunction (IIa, B). CDH is characterized by marked lung hypoplasia and severe PH that is often accompanied by left ventricular (LV) systolic or diastolic dysfunction. The presence of severe PH is a critical determinant of survival in infants with CDH, with high prevalence (63%) and mortality (45%). PVR can persist at suprasystemic levels in newborns with CDH, causing right-to-left extrapulmonary shunt across the foramen ovale and ductus arteriosus, resulting in PPHN physiology and profound hypoxemia. Case reports have suggested that iNO therapy can improve oxygenation and pulmonary hemodynamics in infants with CDH and severe PH, reducing the need for ECMO therapy; however, this was not proven in a randomized trial. In infants with CDH, severe PH, and suspected LV dysfunction, iNO therapy may contribute to pulmonary edema. With close monitoring of oxygenation and hemodynamics, a brief trial of iNO therapy to assess for benefits in severe CDH is suggested. If ECMO is being initiated, iNO therapy may allow for a safer transition to ECMO in CDH. Lack of improvement may be related to LV dysfunction or poor lung recruitment. This recommendation places a high value on preventing the need for an invasive therapy that is potentially harmful, burdensome, and costly and a lower value on the potential side effects of iNO therapy.

Recommendation 2: Evaluation for chronic PAH-specific therapy in infants with CDH who have PH should follow recommendations for all children with PH, and thus includes cardiac catheterization (I, B). Sustained elevation of PAP, above two-thirds systemic pressure, is strongly associated with high mortality in patients with CDH. High PVR in CDH is caused by multiple factors, including increased vascular tone, hypertensive remodeling, reduced vascular surface area, and a high rate of vascular anomalies. In addition, LV dysfunction can further contribute to elevated PAP in severe CDH. As a result, serial echocardiograms can be helpful in CDH management, but, in addition, cardiac catheterization may identify cardiopulmonary abnormalities that contribute to the severity of PH in subjects with CDH. Identification of such comorbidities may lead to therapy that mitigates the PH. Even if contributing comorbidities are not identified, confirmation of the PH, assessment of its severity, and determination of the potential role for LV dysfunction will affect the decision of whether to institute PAH-specific drug therapy. This recommendation places a high value on identifying contributing factors that can be identified and potentially treated as well as confirming PH before the initiation of PAH-specific therapies that improve outcomes; it places a lower value on the burdens, costs, and adverse consequences of diagnostic testing.

BPD

Recommendation 1: Screening for PH by echocardiogram is recommended in infants with established BPD (I, B). The Committee recommends 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, intrauterine growth restriction, and extreme prematurity. Similarly, infants with BPD with a particularly slow rate of clinical improvement, as manifested by a persistent or increasing need for high levels of respiratory support, should be assessed for PH. Preterm infants who require supplemental oxygen or positive pressure ventilation support at 36 weeks corrected age, have oxygen needs at levels disproportionate to their degree of lung disease, or have recurrent cyanotic episodes warrant evaluation for PH and other cardiovascular sequelae. Echocardiography may also guide the clinician as to the need for and choice of advanced testing modalities, such as cardiac catheterization, cardiac magnetic resonance imaging, or chest computed tomography scan, thereby reducing patient harm and the cost of unnecessary testing. The recommendation places a high value on early diagnosis and treatment; it places a lower value on the consequences of misleading test results and the burdens and costs of diagnostic testing.

Recommendation 2: Evaluation and treatment of lung disease, including assessments for hypoxemia, aspiration, structural airway disease, and the need for changes in respiratory support, is recommended in infants with BPD and PH before initiation of PAH-targeted therapy (I, B). Respiratory-based therapies that improve lung function and gas exchange can lower PH in infants with BPD, which may either eliminate or reduce the need for or amount of PAH-specific drug therapy and reduce the potential side effects and costs of these therapies. Intermittent or prolonged hypoxia can cause or delay the resolution of persistent PH in BPD, and targeting oxygen saturations to 92 to 94% is generally sufficient to prevent the adverse effects of hypoxia on PH in most infants without increasing the risk of additional lung inflammation and injury. This recommendation places a high value on identifying and treating underlying lung disease to both improve clinical outcomes and reduce the need for potentially harmful, costly, and burdensome PAH-specific therapy. This approach places a lower value on the potential harms, burdens, and costs of the diagnostic evaluation and interventions directed toward identifying and ameliorating conditions that contribute to the underlying lung disease, such as chronic reflux and aspiration, structural airway abnormalities (such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, tracheomalacia, and other lesions), bronchial reactivity, and others.

Recommendation 3: Evaluation for chronic PAH-specific drug therapies 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 (I,B). In patients with PH by echocardiogram, the committee recommends cardiac catheterization for patients with BPD who: (*1*) have persistent signs of severe cardiorespiratory disease or clinical deterioration not directly related to airway disease; (*2*) are suspected of having significant PH despite optimal management of their lung disease and associated morbidities; (*3*) are candidates for chronic PH drug therapy; and (*4*) have unexplained, recurrent pulmonary edema. The goals of cardiac catheterization are to assess the severity of PH; exclude or document the severity of associated anatomic cardiac lesions; define the presence of systemic-pulmonary collateral vessels, pulmonary vein stenosis, or LV diastolic dysfunction; assess pulmonary vascular reactivity in patients who fail to respond to oxygen therapy alone; and determine the physiologic impact of anatomic shunt lesions that are commonly present. Importantly, elevated pulmonary capillary wedge or left atrial pressure may signify LV diastolic dysfunction, which can contribute to PH, recurrent pulmonary edema, or poor iNO responsiveness in infants with BPD. This recommendation places a high value on identifying contributing factors that can be treated as well as to confirming the severity and etiology of PH before the initiation of PAH-specific therapies that improve outcomes. It places a lower value on the burdens, costs, and adverse consequences of cardiac catheterization, but, as discussed above, cardiac catheterization in infants with severe BPD and PH should only be performed by experienced teams of PH experts.

Pharmacotherapy

Recommendation 1: Chronic anticoagulation with warfarin may be considered in patients with IPAH/heritable PAH, low cardiac output, chronic indwelling catheter, and hypercoagulable states (IIb, C).

i. Targeting the therapeutic range for INR between 1.5 and 2.0 is recommended for young children with PAH (I, C).

ii. Anticoagulation should not be used in young children with PAH due to concerns for harm from hemorrhagic complications (III, C).

In patients with IPAH/heritable PAH, low cardiac output, a chronic indwelling catheter, or a hypercoagulable state, anticoagulation is associated with lower mortality. However, anticoagulation in young children is generally not recommended unless the child has a central line or is hypercoagulable. Difficulty in maintaining international normalized ratio (INR) at the target range, and its use in children before being able to walk well due to developmental issues or neurologic problems, increases the risk for serious bleeding complications. This recommendation places a high value on decreasing mortality and a lower value on hemorrhagic complications. Compared with an INR less than 1.5 or greater than 2.0, an INR between 1.5 and 2.0 is associated with fewer thromboembolic or bleeding events, respectively. Concerns persist, however, regarding the use of anticoagulation in young infants and children.

Recommendation 2: Intravenous and subcutaneous prostacyclin or its analogs should be initiated without delay for patients with higher-risk PAH, especially with functional class IV disease (I, B). In children with higher-risk PAH, especially those who fail to respond to oral or inhalational PAH-specific therapies, intravenous and subcutaneous prostacyclin analogs can improve survival and quality of life. Prostacyclin analogs are associated with nausea, diarrhea, jaw pain, bone pain, and headaches. In addition, these agents are

expensive, and systemic administration can be burdensome and associated with catheter-related complications, such as infection and thrombosis. This recommendation places a high value on improving clinical outcomes and a lower value on convenience, adverse effects, and costs.

Pediatric Heart Disease

Recommendation 1: In children with significant structural heart disease (i.e., atrial septal defect, ventricular septal defect, and PDA) who have not undergone early repair (as generally defined by age 1–2 yr, depending on the lesion and overall clinical status):

i. Cardiac catheterization should be considered to measure PVRI and determine operability (II, B).

ii. Repair should be considered if PVRI is less than 6 WU · m^2 or PVR/SVR less than 0.3 at baseline (I, B).

Cardiac catheterization provides direct measurements of PVRI and transpulmonary pressure gradients, which are used to identify patients for whom surgical correction of the structural heart disease will improve survival. Complications of cardiac catheterization include respiratory depression due to the sedation, pneumothorax, arrhythmias, cardiac or vascular perforation, and bleeding. Surgical correction in subjects when the PVRI is less than 6 WU · m^2 or PVR/SVR is less than 0.3 improves survival. Surgical repair is associated with postoperative complications such as bleeding, atelectasis, hypoxemia, infection, prolonged respiratory failure, and pain. When compared with a lower PVRI and PVR/SVR threshold to identify operable patients, the Committee's recommended thresholds are more likely to allow surgery on patients in whom higher risks exceed the benefits. This recommendation places a high value on the identification of patients who will benefit from surgical correction. This recommendation places a lower value on the complications of cardiac catheterization or on the possibility of operating on every patient who might benefit from surgical correction, regardless of operative risk. Patients in whom the PVRI is greater than 6 WU · m^2, the PVR/SVR is greater than 0.3, and AVT is negative are less likely to benefit from surgical correction. The decision to not operate on such patients decreases the likelihood of unnecessary postoperative complications, including bleeding, atelectasis, hypoxemia, infection, prolonged respiratory failure, and pain. By not offering surgery to patients in whom the PVRI is greater than 6 WU · m^2, the PVR/SVR is greater than 0.3, and AVT does not reverse the PAH, a few patients who would have benefitted from the operations will be missed. This recommendation places a high value on avoiding unnecessary postoperative complications and a lower value on ensuring that no patient who may benefit will be missed. It also places a lower emphasis on the risks of cardiac catheterization and AVT.

Lung Diseases

Recommendation 1: Children with chronic diffuse lung disease should be evaluated for concomitant cardiovascular disease or PH by echocardiogram, especially with advanced disease (I, B). Patients with chronic diffuse lung disease have diminished exercise capacity, respiratory symptoms and signs, and increased mortality. These respiratory signs are also characteristic of adverse physiologic effects of PH. As a result, echocardiography can help determine whether or not PH may also be contributing to the patient's symptoms, especially when performed with exercise testing. Echocardiography further identifies anatomic cardiac abnormalities or dysfunction, for which medical therapy improves clinical outcomes. Echocardiography may guide the clinician to further testing, such as right heart catheterization, which can assess the severity of PH, vascular reactivity, and the presence of unsuspected cardiopulmonary problems, such as collateral vessels, abnormal vascular structure, and cardiac dysfunction. Finding severe PH would lead to earlier and more aggressive treatment, which may improve clinical outcomes. This recommendation places a high value on the potential impact of early identification of significant PH and myocardial performance and places a lower value on the burdens and costs of echocardiography.

Recommendation 2: For exercise-limited patients with advanced lung disease and evidence of PH, a trial of PAH-targeted therapy is reasonable (IIa, C), and right heart catheterization may be considered (IIb,B). In patients with advanced lung disease and PH, PAH-specific drug therapy can improve exercise tolerance, respiratory symptoms and signs, and quality of life. PAH-specific drug therapy can worsen oxygenation in some patients with chronic lung disease; this is generally a small change in oxygenation and is readily treated with small increases in supplemental oxygen therapy. This recommendation places high value on improving clinical outcomes and a lower value on the potential side effects of therapy. In patients with advanced lung disease and PAH, right heart catheterization can (*1*) determine the severity of the underlying PH; (*2*) test for acute vasoreactivity to help guide drug therapy; and (*3*) seek evidence of additional contributors to the PH, such as left heart disease, structural vascular disorders, and pulmonary venoocclusive disease. Cardiac catheterization in patients with advanced lung disease includes several risks, such as hypoxemia, hypercarbia, PH crisis, bleeding, pneumothorax, cardiac or vascular perforation, arrhythmia, and cardiac arrest. Risks for AVT include acute pulmonary edema in the presence of cardiomyopathy or pulmonary venoocclusive disease. This recommendation places a high value on accurately determining the presence and severity of PH before initiation of PAH-specific therapy over the potential risks of starting empiric therapy without better characterization of the underlying PH.

PH in Sickle Cell Disease

Recommendation 1: Children with sickle cell disease who have evidence of PH by echocardiography should undergo further cardiopulmonary evaluation, including pulmonary function testing, polysomnography, assessment of oxygenation, and evaluation for thromboembolic disease (I, C). Echocardiographic findings of PH in sickle cell disease (SCD) provide a useful biomarker or surrogate endpoint that suggests high SCD-related mortality and morbidity. In addition to PVD, echocardiographic signs of PH in SCD may reflect SCD-related abnormalities without PVD, including severe anemia, high cardiac output, or iron overload (hemochromatosis). Because SCD can have associated lung disease, the finding of PH by echocardiogram may be due to intermittent

or sustained hypoxia due to sleep-disordered breathing, chronic interstitial lung disease, chronic obstructive lung disease, or thromboembolic disease. Identification of an underlying cause for PH in SCD may lead to targeted therapy that offers the potential to improve cardiopulmonary symptoms. By identifying precipitating or exacerbating factors that can be corrected, one may prevent or reduce the need for PAH-specific therapies, which can be harmful, burdensome, and costly. Recommendations include formal pulmonary function testing, polysomnography, and assessment of oxygenation, which are not harmful, overly burdensome, or costly. This recommendation places a high value on identifying the underlying cause of the PH and initiating therapy that improves clinical outcomes and decreases the need for PAH-specific therapy. This recommendation places a lower value on the undesirable consequences of misleading results, burdens, and costs of diagnostic testing.

Recommendation 2: Children with SCD should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (I, C), and PAH-targeted therapy should not be used empirically in SCD-associated PH because of potential adverse effects (III, C). In patients with SCD, right heart catheterization can determine the severity of the underlying PH and elucidate whether PH is due to anemia, high cardiac output, left ventricular dysfunction, or intrinsic PVD. Catheterization may lead to interventions that are more specific and less expensive, harmful, and burdensome. This recommendation places a high value on identifying the underlying cause of the PH and initiating therapy directed at the underlying cause to improve clinical outcomes and avoid the unnecessary use of PAH-specific therapy. It would reserve PAH-specific therapy for those with high PVR and normal pulmonary capillary wedge pressure. This recommendation recognizes that off-label use of PAH-specific therapies can be harmful, burdensome, and costly and places a lower value on the harms of cardiac catheterization and AVT. Because echocardiographic signs of PH may not be related to PVD in subjects with SCD, PAH-specific therapy should not be empirically used without a full evaluation. In addition, some PAH-specific drugs may be harmful in patients with SCD, as reported in a clinical trial of sildenafil therapy for SCD that demonstrated an increased risk for vasoocclusive disease and acute chest syndrome in patients with SCD with PH. Using PAH-specific therapy only in the setting of right heart catheterization–confirmed PH reduces the frequency of side effects due to inappropriate therapy. This recommendation places a high value on not causing harmful effects from PAH-specific therapy in patients who are unlikely to benefit from therapy and places less value on the risk that some PAH drugs might have benefit in SCD-associated PH.

Outpatient Care of Children with PH

Recommendation 1: Children with PH should be evaluated and treated in comprehensive, multidisciplinary clinics at specialized pediatric centers (I, C). Interdisciplinary teams, including pediatric cardiology, pulmonology, neonatology, critical care, and others, including social workers, psychologists, and physiotherapists, can provide the necessary expertise and experience in approaching the diverse causes of PH in children. This recommendation places high value on patient safety and satisfaction, recognizing the ability of an experienced team to best meet the diverse, ongoing needs of patients with PH and their families. The recommendation puts a lower value on the time demands on clinicians or challenges with the fiscal implications of building and maintaining such teams.

Recommendation 2: 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 (I, C). Children with PH are at risk for sudden death or respiratory and cardiac arrest due to PH crisis, even with routine anesthesia during elective procedures. Providers with experience in pediatric PH can provide the necessary expertise and experience in preventing and managing the diverse complications of surgery in children with PH. This likely prevents complications and improves clinical outcomes. Receiving care at an experienced center reduces risk but can be burdensome if the center is located far from the patient's home. This recommendation places high value on patient safety and a lower value on burden.

Recommendation 3: Because of the risks of syncope or sudden death with exertion, it is recommended that a thorough evaluation, including cardiopulmonary exercise testing and treatment, be performed before engaging in athletic ("symptom-limited") activities (I, C). Children with PH have increased risk of syncope and sudden death with exertion. Physiologic studies including exercise testing may help determine the risk of such events and/or the maximum level of safe exercise, which helps advise patients and their families. Instructing patients and families on safe exercise reduces the risk of poor clinical outcomes. Discussion of physical limitations may be difficult for some patients or their families and may cause distress if not handled in a respectful and sensitive fashion. This recommendation places a high value on avoiding life-threatening complications of exercise and a lower value on the burdens and psychological effects of counseling.

Recent Advances in Pediatric Pulmonary Hypertension

Since completion of the work of the AHA/ATS Joint Guidelines Committee, numerous publications have been published that continue to rapidly advance the goals of improving the care and outcomes of children with PVD. Many diverse and wide-ranging studies have further increased our knowledge, which include examples of studies involving epidemiologic data from patient registries (17, 19–22); diagnostic strategies, including the role of cardiac catheterization and AVT (23, 24); insights into the genetics and molecular strategies for precision medicine in PAH (25–27); and pediatric-specific approaches toward monitoring disease progression with novel endpoints (28–30) and interventions (31). More recently, others have formed teams to make recommendations for care guidelines, such as those recently published by European investigators (32).

Conclusions

Pediatric PH has significant adverse effects on long-term outcomes in diverse settings, yet information on how to best diagnose and manage PVD in children remains limited.

Although associated with relatively rare disorders, growing recognition of the critical impact of PH in children has led to increased awareness of the need for more basic, translational, and population studies to fill knowledge gaps in the field. The development of guidelines for the care of children with PH is intended to provide current recommendations from experts in the field; in addition, these are especially important for highlighting important needs and stimulating further research in the field. Future work along these lines will likely lead to substantial revision of such guidelines, further improving the clinical outcomes of children with PH. Finally, we would further emphasize the importance of developing strategies that promote the successful transition of adolescents with PH from pediatric to adult programs to optimize the continuity of care of pediatric patients into their adult years. ■

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