Pediatric Pulmonary Hypertension

D. Dunbar Ivy, MD,* Steven H. Abman, MD,† Robyn J. Barst, MD,‡ Rolf M. F. Berger, MD,§ Damien Bonnet, MD,ǁ Thomas R. Fleming, PhD,¶ Sheila G. Haworth, MD,#$ J. Usha Raj, MD,** Erika B. Rosenzweig, MD,† Ingram Schulze Neick, MD,# Robin H. Steinhorn, MD,†† Maurice Beghetti, MD‡‡

Aurora, Colorado; New York, New York; Groningen, the Netherlands; Paris, France; Seattle, Washington; London, United Kingdom; Chicago, Illinois; Davis, California; and Geneva, Switzerland

Pulmonary hypertension (PH) is a rare disease in newborns, infants, and children that is associated with significant morbidity and mortality. In the majority of pediatric patients, PH is idiopathic or associated with congenital heart disease and rarely is associated with other conditions such as connective tissue or thromboembolic disease. Incidence data from the Netherlands has revealed an annual incidence and point prevalence of 0.7 and 4.4 for idiopathic pulmonary arterial hypertension and 2.2 and 15.6 for pulmonary arterial hypertension, respectively, associated with congenital heart disease (CHD) cases per million children. The updated Nice classification for PH has been enhanced to include a greater depth of CHD and emphasizes persistent PH of the newborn and developmental lung diseases, such as bronchopulmonary dysplasia and congenital diaphragmatic hernia. The management of pediatric PH remains challenging because treatment decisions continue to depend largely on results from evidence-based adult studies and the clinical experience of pediatric experts. (J Am Coll Cardiol 2013;62:D117–26) © 2013 by the American College of Cardiology Foundation

Pulmonary hypertension (PH) can present at any age from infancy to adulthood. The distribution of etiologies in children is quite different than that of adults, with a predominance of idiopathic pulmonary arterial hypertension (IPAH) and PAH associated with congenital heart disease (PAH-CHD) (1–5). In pediatric populations, IPAH is usually diagnosed in its later stages due to nonspecific symptoms. Without appropriate treatments, median survival rate after diagnosis of children with IPAH appears worse when compared with that of adults (6). Therapeutic strategies for adult PAH have not been sufficiently studied in children, especially regarding potential toxicities, formulation, or optimal dosing, and appropriate treatment targets for goal-oriented therapy in children are lacking. Nevertheless, children with PAH are currently treated with targeted PAH drugs and may benefit from these new therapies. This review provides an overview of recent information regarding the current approach and diagnostic classification of PAH in children as based on discussions and recommendations from the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension (WSPH) in Nice, France (2013).

Definition

The definition of PH in children is the same as that in adults. Similar to adults, pulmonary vascular resistance (PVR) is increased. PH is further defined by the Younger classification as primary or secondary, and the size of the pulmonary arteries as small, medium, or large. Primary PH is defined as a right ventricular pressure of 50 mm Hg or greater with the absence of a known cause of PH. Secondary PH is defined as the result of a known cause of PH, such as left heart disease, congenital heart disease, connective tissue disease, or chronic thromboembolic disease. The size of the pulmonary arteries is determined by the percentage of the pulmonary arterial diameter that is less than the abdominal aortic diameter. Small pulmonary arteries are defined as pulmonary arterial diameters less than 2 mm, medium pulmonary arteries as diameters between 2 mm and 4 mm, and large pulmonary arteries as diameters greater than 4 mm.

From *Pediatric Cardiology, Children’s Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado; †Pediatric Pulmonary Medicine, Children’s Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado; ‡Columbia University, College of Physicians and Surgeons, New York, New York; §Centre for Congenital Heart Diseases, Pediatric Cardiology, Beatrix Children’s Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ǁCentre de Référence Malformations Cardiaques Congénitales Complexes, Necker Hospital for Sick Children, Assistance Publique des Hôpitaux de Paris, Pediatric Cardiology, University Paris Descartes, Paris, France; ¶Department of Biostatistics, University of Washington, Seattle, Washington; #Great Ormond Street Hospital, London, United Kingdom; **Department of Pediatrics, University of Illinois at Chicago, Chicago, Illinois; ††Department of Pediatrics, University of California Davis Children’s Hospital, Davis, California; and the ‡‡Pediatric Cardiology Unit, University Hospital, Geneva, Switzerland. The University of Colorado School of Medicine has received consulting fees for Dr. Ivy from Actelion, Bayer, Gilead, Eli Lilly, Pfizer, and United Therapeutics. The University Medical Center Groningen has received consulting fees for Dr. Berger from Actelion, Bayer, GlaxoSmithKline, Lilly, Novartis, and Pfizer. Dr. Berger has performed consultancies for Actelion, Bayer, GlaxoSmithKline, Lilly, Novartis, Pfizer, and United Therapeutics. Dr. Bonnet has received lecture and consulting honoraria from Actelion, Eli Lilly, Pfizer, and Bayer. Dr. Fleming has served as a consultant to Actelion and Pfizer. Dr. Haworth has received consulting fees from GlaxoSmithKline. Dr. Rosenzweig has received research grant support from Actelion, Gilead, GlaxoSmithKline, Eli Lilly, Bayer, and United Therapeutics; and consulting honoraria from United Therapeutics and Actelion. The University of California has received consulting fees for Dr. Steinhorn from Ikaria and United Therapeutics, and she has served as an unpaid consultant to Actelion. Dr. Beghetti has served as an advisory board member for Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, and Pfizer; has received grants from Actelion and Bayer; has receiving lecture fees from Actelion, Bayer, and Pfizer; has developed educational materials for Actelion and Pfizer; and has receiving consulting fees from Actelion, Bayer, GlaxoSmithKline, Pfizer, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 15, 2013; accepted October 22, 2013.
in response to AVT that determines operability with adequate sensitivity and specificity to predict a favorable long-term outcome. The preponderance of data used for evaluation of operability includes baseline hemodynamics and clinical characteristics (15). In assessing prognosis in IPAH and repaired CHD, AVT may be predictive. The Barst and Sitbon criteria have each been shown to be of predictive value in IPAH in children and adults (12,16,17).

**Classification**

As a modification of the past Dana Point classification (18), the Nice clinical classification of PH further highlights aspects of pediatric disorders, especially in regard to childhood disorders that may be increasingly encountered by specialists treating adults with PH (Table 1). Children with PH who were diagnosed in the neonatal through adolescent age ranges are now surviving into adulthood; thus, a common classification is required to facilitate transition from pediatric to adult services. In addition, goals for improving pediatric classification systems include the need for clarification of disease phenotype, encouraging new thinking on causation and disease pathobiology, enhancement of diagnostic evaluations, improvements in correlations of phenotype and therapeutic responsiveness, and enhancement of clinical trial design. As a result, the Pediatric Task Force recommended several changes for implementation in the WSPH meeting proceedings.

In particular, the Nice classification now includes additional novel genetic disorders causing PAH, including those related to mutations in the following genes: SMAD 9, cavolin 1 (19), potassium channel KCNK3 (20), and T-box 4 (small patella syndrome) (21).

Persistent pulmonary hypertension of the newborn (PPHN), due to its particular anatomic and physiological nature, has been moved to a separate subcategory in group 1 to emphasize unique aspects of its timing of onset immediately after birth, time course, and therapeutic strategies. In group 2, congenital and acquired left heart inflow and outflow tract obstruction has been added (22). Lesions in this category include pulmonary vein stenosis, cor triatriatum, supravalvular mitral ring, mitral stenosis, subaortic stenosis, aortic valve stenosis, and coarctation of the aorta associated with an increased left ventricular end-diastolic pressure. In group 3, developmental lung diseases have been emphasized due to growing recognition of the important role of abnormal lung vascular growth in the pathogenesis of PH and impaired lung structure in these disorders (Table 2). Congenital diaphragmatic hernia (CDH) and bronchopulmonary dysplasia (BPD) (Fig. 1) have been highlighted due to their relative frequency and the critical role of PH in determining survival and long-term outcomes (23–25). Several other developmental disorders, such as surfactant protein deficiencies and alveolar capillary dysplasia, are now included as relatively rare but important causes of PH (Table 2). In the neonate, these
CHD of any type who develop PHVD. The task force also recognized lesions in which pulmonary vascular disease is likely, but the specific criteria for PH are not met, and thus are not included in the Nice clinical classification. This includes patients with single ventricle physiology who have undergone bidirectional Glenn or Fontan-type procedures. In this setting of nonpulsatile flow to the pulmonary arteries, PAP may not be >25 mm Hg; however, significant pulmonary vascular disease can lead to a poor outcome. It is anticipated that these recommended changes in the classification of PH will prove to be useful in the diagnostic evaluation and care of patients and design of clinical trials in pediatric PH.

### Etiology

Current registries have begun to examine the etiology and outcome of pediatric PH. In children, idiopathic PAH, heritable PAH, and APAH-CHD constitute the majority of cases, whereas cases of PAH associated with connective tissue disease are relatively rare. Large registries of pediatric PH, including the TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry and the combined adult and pediatric U.S. REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry, have been described. Of 362 patients with confirmed PH in the TOPP registry, 317 (88%) had PAH, of which 57% were characterized as IPAH or hereditary PAH (HPAH) and 36% as APAH-CHD. PH associated with respiratory disease was also noted, with BPD reported as the most frequent chronic lung disease associated with PH. Only 3 patients had either chronic thromboembolic PH or miscellaneous causes of PH. Chromosomal anomalies (mainly trisomy 21) or syndromes were reported in 47 of the patients (13%) with confirmed PH. Many factors may contribute to PH associated with Down syndrome, such as lung hypoplasia, alveolar simplification (which may be worse in the presence of CHD), CHD, changes in the production and secretion of pulmonary surfactant,
elevated plasma levels of asymmetric dimethyl arginine, hypothyroidism, obstructive airway disease, sleep apnea, reflux, and aspiration (29–31).

Another large registry for pediatric PH has been reported from the nationwide Netherlands PH Service (32). In this registry, 2,845 of 3,263 pediatric patients with PH had PAH (group 1), including transient PAH (82%) and progressive PAH (5%). The remaining causes of PH included lung disease and/or hypoxemia (8%), PH associated with left heart disease (5%), and chronic thromboembolic PH (<1%). The most common causes of transient pulmonary hypertension were PPHN (58%) and APAH-CHD (42%). In the progressive PAH cases, APAH-CHD (72%) and IPAH (23%) were common causes. Down syndrome was the most frequent chromosomal disorder (12%), a rate similar to that observed in the TOPP registry. Thus, early registry reports of children with PH provide important insights into the spectrum of pediatric PH; however, these data are likely limited or biased by the nature of referrals and the clinical practice of PH centers participating in the registries (33).

Epidemiology and Survival

Although the exact incidence and prevalence of PH in pediatric population are still not well known, recent registries have described estimates of incidence and prevalence in children with PAH. In the Netherlands registry, the yearly incidence rates for PH were 63.7 cases per million children. The annual incidence rates of IPAH and APAH-CHD were 0.7 and 2.2 cases per million, respectively. The point prevalence of APAH-CHD was 15.6 cases per million. The incidences of PPHN and transient PH associated with CHD were 30.1 and 21.9 cases per million children, respectively (32). Likewise, the incidence of IPAH in the national registries from the United Kingdom was 0.48 cases per million children per year, and the prevalence was 2.1 cases per million (34).

Prior to the availability of targeted PAH therapies, a single-center cohort study showed that the estimated median survival of children and adults with IPAH were similar (4.12 vs. 3.12 years, respectively) (35). Currently, with targeted pulmonary vasodilators, the survival rate has continued to improve in pediatric patients with PAH. Patients with childhood-onset PAH in the combined adult and pediatric U.S. REVEAL registry demonstrated 1-, 3-, and 5-year estimated survival rates from diagnostic catheterization of 96 ± 4%, 84 ± 5%, and 74 ± 6%, respectively (3). There was no significant difference in 5-year survival between IPAH/FPAH (75 ± 7%) and APAH-CHD (71 ± 13%). Additionally, a retrospective study from the United Kingdom has shown the survival in 216 children with IPAH and APAH-CHD (1). The survival rates of IPAH were 85.6%, 79.9%, and 71.9% at 1, 3, and 5 years, respectively, whereas APAH-CHD survival rates were 92.3%, 83.8%, and 56.9% at 1, 3, and 5 years, respectively. In a separate report of IPAH from the United Kingdom, survival at 1, 3, and 5 years was 89%, 84%, and 75%, whereas transplant-free survival was 89%, 76%, and 57% (34). Reports from the Netherlands have shown 1-, 3-, and 5-year survival of 87%, 78%, and 73%, respectively, for patients with progressive PAH (36). Although overall survival has improved, certain patients, such as those with repaired CHD and PHVD, remain at increased risk (1,32,36,37).
Diagnosis

A methodical and comprehensive diagnostic approach is important because of the many diseases associated with PH. Despite this, recent registries have shown that most children do not undergo a complete evaluation (38–40). A modified, comprehensive diagnostic algorithm is shown in Figure 2. Special situations may predispose to the development of PAH and should be considered (41).

Treatment Goals

Although many treatment goals and endpoints for clinical trials are similar in adults and children, there are also important differences. As in adults, clinically meaningful endpoints include clinically relevant events such as death, transplantation, and hospitalization for PAH. Further parameters that directly measure how a patient feels, functions, and survives are meaningful and include functional
class and exercise testing; however, there are no acceptable surrogates in children. Although World Health Organization (WHO) functional class is not designed specifically for infants and children, it has been shown to correlate with 6-min walk distance and hemodynamic parameters (1–3,32,34). Further, WHO functional class has been shown to predict risk for PAH worsening and survival in pediatric PH of different subtypes. Although not validated, a functional class designed specifically for children has been proposed (42). Pediatric PAH treatment goals may be divided into those that are for patients at lower risk or higher risk for death (Table 4). As in adults, clinical evidence of right ventricular failure, progression of symptoms, WHO functional class 3/4 (3,34,43), and elevated brain natriuretic peptide levels (44–46) are recognized to be associated with higher risk of death. In children, failure to thrive has been associated with higher risk of death (3,34). Abnormal hemodynamics are also associated with higher risk, but the values found to be associated with higher risk are different than those for adults. Additional parameters include the ratio of PAPm to systemic artery pressure, right atrial pressure >10 mm Hg, and PVR index (PVRI) greater than 20 Wood units × m² (16,43). In recent pediatric PAH outcome studies, baseline 6-min walk distance was not a predictor of survival, neither when expressed as an absolute distance in meters nor when adjusted to reference values expressed as z-score or as percentage of predicted value (1,34,36,46,47). Serial follow-up of cardiac catheterization in pediatric PH may be beneficial. Maintenance of a vasoreactivity has been shown to correlate with survival (3,12,16). Indications for repeat cardiac catheterization in children with PH include clinical deterioration, assessment of treatment effect, detection of early disease progression, listing for lung transplant, and prediction of prognosis. However, it must be emphasized that cardiac catheterization should be performed in experienced centers able to manage potential complications such as PH crisis requiring extracorporeal membrane oxygenation (40,48–50). Noninvasive endpoints to be further evaluated in children include pediatric functional class as well as z-scores for body mass index (3,34), echocardiographic parameters such as the systolic to diastolic duration ratio (51), tissue Doppler indexes (52–54), eccentricity index (52), tricuspid plane annular excursion (52,55), and pericardial effusion. Pediatric reference values for cardiopulmonary exercise testing in association with outcome are needed (56,57). Development of assessment tools for daily activity measures may be valuable in determining treatment goals. Initial magnetic resonance imaging parameters are promising (58), and pulsatile hemodynamics such as pulmonary arterial capacitance (59,60) require further validation. Novel parameters, such as fractal branching (61), proteomic approaches (62,63), and definition of progenitor cell populations (64–66) are under active study.

**Treatment**

The prognosis of children with PAH has improved in the past decade owing to new therapeutic agents and aggressive...
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We propose a pragmatic treatment algorithm based on the strength of expert opinion that is most applicable to children with IPAH (Fig. 3). Treatment of PPHN has recently been reviewed (67,68).

The ultimate goal of treatment should be improved survival and allowance of normal activities of childhood without the need to self-limit. The Nice pediatric PH treatment algorithm was modeled from the 2009 consensus adult PH treatment algorithm and current pediatric experience (69). Background therapy with diuretics, oxygen, anticoagulation, and digoxin should be considered on an individual basis. Care should be taken to not overly decrease intravascular volume due to the pre-load dependence of the right ventricle. Following the complete evaluation for all causes of PH, AVT is recommended to help determine therapy.

In children with a positive AVT response, oral CCBs may be initiated (12,70). Therapy with amlodipine, nifedipine, or diltiazem has been used. Because CCBs may have negative inotropic effects in young infants, these agents should be avoided until the child is older than 1 year of age. In the child with a sustained and improved response, CCBs may be continued, but patients may deteriorate, requiring repeat evaluation and additional therapy. For children with a negative acute vasoreactivity response or in the child with a failed or nonsustained response to CCBs, risk stratification should determine additional therapy (Table 4). Although the specific number of lower- or higher-risk criteria to drive therapeutic choices is not yet known, a greater proportion of either should be considered as justification for therapy. Similar to adults, determinants of higher risk in children include clinical evidence of right ventricular failure, progression of symptoms, syncope, WHO functional class III or IV, significantly elevated or rising B-type natriuretic peptide levels, severe right ventricular enlargement or dysfunction, and pericardial effusion. Additional hemodynamic parameters that predict higher risk include a PAPm to systemic artery pressure ratio >0.75 (16), right atrial pressure >10 mm Hg, and PVRI greater than 20 Wood units x m⁻² (43). Additional high-risk parameters include failure to thrive. In the child with a negative acute vasoreactivity response and lower risk, initiation of oral monotherapy is recommended. Treatment of choice is an endothelin receptor antagonist (bosentan [43,71–77], ambrisentan [78,79]) or phosphodiesterase 5 (PDE5) inhibitor (sildenafil [80–86], tadalafil [87,88]). The STARTS-1 (Sildenafil in Treatment-Naive Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension) and STARTS-2 sildenafil trials have received recent regulatory attention and were actively discussed at the WSPH meeting. STARTS-1 and STARTS-2 were worldwide randomized (stratified by weight and ability to exercise), double-blind, placebo-controlled studies of treatment-naive children with PAH. In these 16-week studies, the effects of oral sildenafil monotherapy in pediatric PAH were studied (84). Children with PAH (1 to 17 years of age; ≥8 kg) received low- (10 mg), medium- (10 to 40 mg), or high- (20 to 80 mg) dose sildenafil or placebo orally 3 times daily. The estimated mean ± standard error percentage change in pVO₂ for the low-, medium- and high-doses combined versus placebo was 7.7 ± 4.0% (95% CI: −0.2% to 15.6%; p = 0.056). Thus, the pre-specified primary outcome measure was not statistically significant. Peak VO₂ only improved with the medium dose. Functional capacity only improved with high dose sildenafil. PVRI improved with medium- and high-dose sildenafil, but mean PAP was lower only with medium-dose sildenafil. As of June 2011, 37 deaths had been reported in the STARTS-2 extension study (26 on study treatment). Most patients who died had IPAH/HPAH and baseline functional class III/IV disease; patients who died had worse baseline hemodynamics. Hazard ratios for mortality were 3.95 (95% CI: 1.46 to 10.65) for high versus low dose and 1.92 (95% CI: 0.65 to 5.65) for medium versus low dose (83). Review of these data by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) resulted in disparate

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<th>Table 4 Pediatric Determinants of Risk</th>
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recommendations. Sildenafil was approved by the EMA in 2011 (10 mg 3 times daily for weight <20 kg and 20 mg 3 times daily for weight >20 kg), with a later warning on avoidance of use of higher doses. In August 2012, the FDA released a warning against the (chronic) use of sildenafil for pediatric patients (ages 1 to 17 years) with PAH.

Children who deteriorate on either endothelin receptor antagonist or PDE5 inhibitor agents may benefit from consideration of early combination therapy (add-on or up front). If the child remains in a low-risk category, addition of inhaled prostacyclin (iloprost [10,89–91], treprostinil [11,92]) to background therapy may be beneficial. It is crucial to emphasize the importance of continuous repeat evaluation for progression of disease in children on any of these therapies. In children who are higher risk, initiation of intravenous epoprostenol (11,12,70,90,93–96) or treprostinil (96,97) should be strongly considered. Experience using subcutaneous treprostinil is increasing as well (98). In the child deteriorating with high-risk features, early consideration of lung transplant is important.

Atrial septostomy may be considered in the child with worsening PAH despite optimal medical therapy but should be considered before the later stages with increased risk (99). Features of a high-risk patient for this procedure include high right atrial pressure and low cardiac output. Atrial septostomy may be considered as an initial procedure or before consideration of lung transplant. Surgical creation of a palliative Potts shunt (descending aorta to left pulmonary artery) has been described as a new option for severely ill children with suprasystemic IPAH (100). Serial reassessment of the response to targeted PAH agents remains a critical part of the long-term care in children with PH. Future clinical trials designed specifically for pediatric patients with PH are essential to further optimize therapeutic guidelines.

Conclusions

The incidence and prevalence of IPAH are lower in children than adults. The Nice classification incorporates the growing population of children with developmental lung diseases, such as BPD and CDH. Recent treatment strategies in children have improved their prognosis over the past decade since the introduction of new therapeutic agents, although almost all are based on experience and cohort studies rather than randomized trials. Future pediatric studies are required for development of specific treatment strategies and clinical endpoints for children with PH.

Reprint requests and correspondence: Dr. Dunbar Ivy, Pediatric Cardiology, Children’s Hospital Colorado, 13123 East 16th Avenue, B100, Aurora, Colorado 80045. E-mail: dunbar.ivy@childrenscolorado.org.

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Key Words: congenital heart disease • pediatrics • pulmonary arterial hypertension