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Pediatric Pulmonary Hypertension

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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 (APAH-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

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Abbreviations and Acronyms

APAH-CHD = pulmonary arterial hypertension associated with congenital heart disease

AVT = acute vasodilator testing

CHD = congenital heart disease

HPAH = hereditary pulmonary arterial hypertension

IPAH = idiopathic pulmonary arterial hypertension

PAPm = mean pulmonary artery pressure

PH = pulmonary hypertension

PHVD = pulmonary hypertensive vascular disease

PPHN = persistent pulmonary hypertension of the newborn

PVR = pulmonary vascular resistance

SVR = systemic vascular resistance

excluded in the definition of PH. Absolute pulmonary artery pressure falls after birth, reaching levels that are comparable to adult values within 2 months after birth. After 3 months of age in term babies at sea level, PH is present when the mean pulmonary pressure exceeds 25 mm Hg in the presence of an equal distribution of blood flow to all segments of both lungs. This definition does not carry any implication of the presence or absence of pulmonary hypertensive vascular disease (PHVD). In particular, PVR is important in the diagnosis and management of PHVD in children with CHD.

In defining the response to acute vasodilator testing (AVT), it is critical to initially determine the purpose of the test for the care of the individual child. Three separate situations may be evaluated. First, AVT is critical for determining possible treatment with calcium channel blockers (CCBs) in patients with IPAH. Second, AVT may be helpful in the assessment of operability in children with CHD. Third, AVT may aid in assessing long-term prognosis. There is no drug standard for AVT in pediatrics; however, inhaled nitric oxide (dose range 20 to 80 parts per million) has been used most frequently and is advised if available for this purpose (3,4,7–11). In the child with IPAH, a robust positive response during AVT may be used to determine whether or not treatment with a CCB may be beneficial. Use of the modified Barst criteria, which is defined as a 20% decrease in mean pulmonary artery pressure (PAPm) with normal or sustained cardiac output and no change or decrease in the ratio of pulmonary to systemic vascular resistance (PVR/SVR) has been associated with a sustained response to CCBs (12). Although generally used in adult settings, evaluation of the Sitbon criteria (e.g., a decrease in PAPm by 10 mm Hg to a value <40 mm Hg with sustained cardiac output) has not been studied adequately in children with IPAH to determine if these criteria are appropriate, in particular with regard to long-term response (13). In assessing operability in CHD, there is no established protocol for AVT or proven criteria for assessing the response with respect to either operability or long-term outcomes (level C). Although many studies have evaluated retrospective criteria for operability, such as PVR/SVR (9,14), there is no solid evidence to support the absolute mean pulmonary pressure, PVR index, or PVR/SVR 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, caveolin 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

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
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 disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*Modified as compared with the Dana Point classification. Reprinted with permission from Simonneau G, Gatzoulis MA, Adatia I. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34–41.

BMPR2 = bone morphogenetic protein receptor type II; CAV1 = caveolin 1; ENG = endoglin; KCNK3 = potassium channel K3; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PPHN = persistent pulmonary hypertension of the newborn.

latter disorders often present with severe or lethal PH and must be specifically evaluated to provide appropriate diagnosis and management. In group 5, the category of segmental PH has been added to PH with unclear multifactorial mechanisms. Examples of segmental PAH include pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries and branch pulmonary arterial stenosis of variable severity.

The Nice classification has also been modified with regard to PAH associated with CHD (Table 3). Type 1 includes patients with classic Eisenmenger syndrome with right-to-left shunting and systemic desaturation. Type 2 includes patients with CHD and significant PHVD with normal resting saturation. The shunts may be either operable or inoperable but are characterized by increased PVR. Type 3 includes PAH with coincidental CHD, which includes small atrial or ventricular septal defects that do not cause severe PAH and follow a course similar to IPAH. Finally, post-operative PAH (type 4) includes patients with repaired

Table 2 Developmental Lung Diseases Associated With Pulmonary Hypertension

Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Alveolar capillary dysplasia (ACD)
ACD with misalignment of veins
Lung hypoplasia (“primary” or “secondary”)
Surfactant protein abnormalities
Surfactant protein B (SPB) deficiency
SPC deficiency
ATP-binding cassette A3 mutation
thyroid transcription factor 1/Nkx2.1 homeobox mutation
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

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 (26). 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 (27). 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 (1–4,28). Large registries of pediatric PH, including the TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry (4) and the combined adult and pediatric U.S. REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry, have been described (3). 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 (4). 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,

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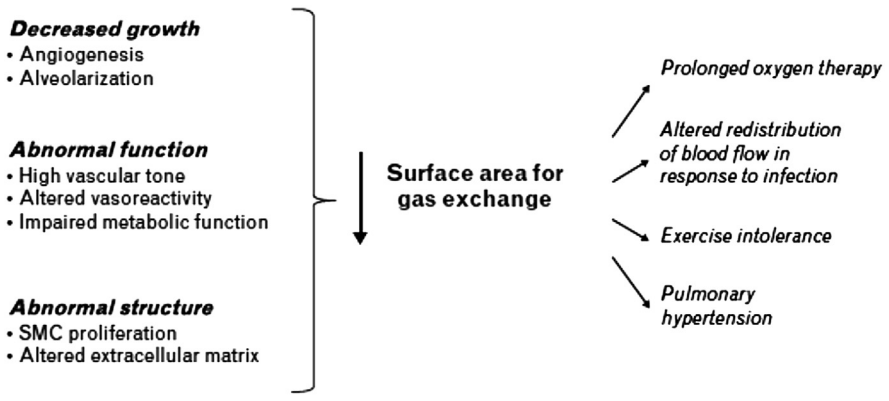

Figure 1 Pulmonary Vascular Disease in Bronchopulmonary Dysplasia

From Mourani PM, Abman SH. Curr Opinion Pediatr 2013;25:329–37. SMC = smooth muscle cell.

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).

Table 3 Clinical Classification of Congenital Heart Disease Associated With Pulmonary Arterial Hypertension

1. Eisenmenger Syndrome
2. Left to right shunts
Operable
Inoperable
3. PAH with co-incidental CHD
4. Post-operative PAH

Definition of PAH based on mean PAP >25 mm Hg and PVR >3 Wood units × m^2.

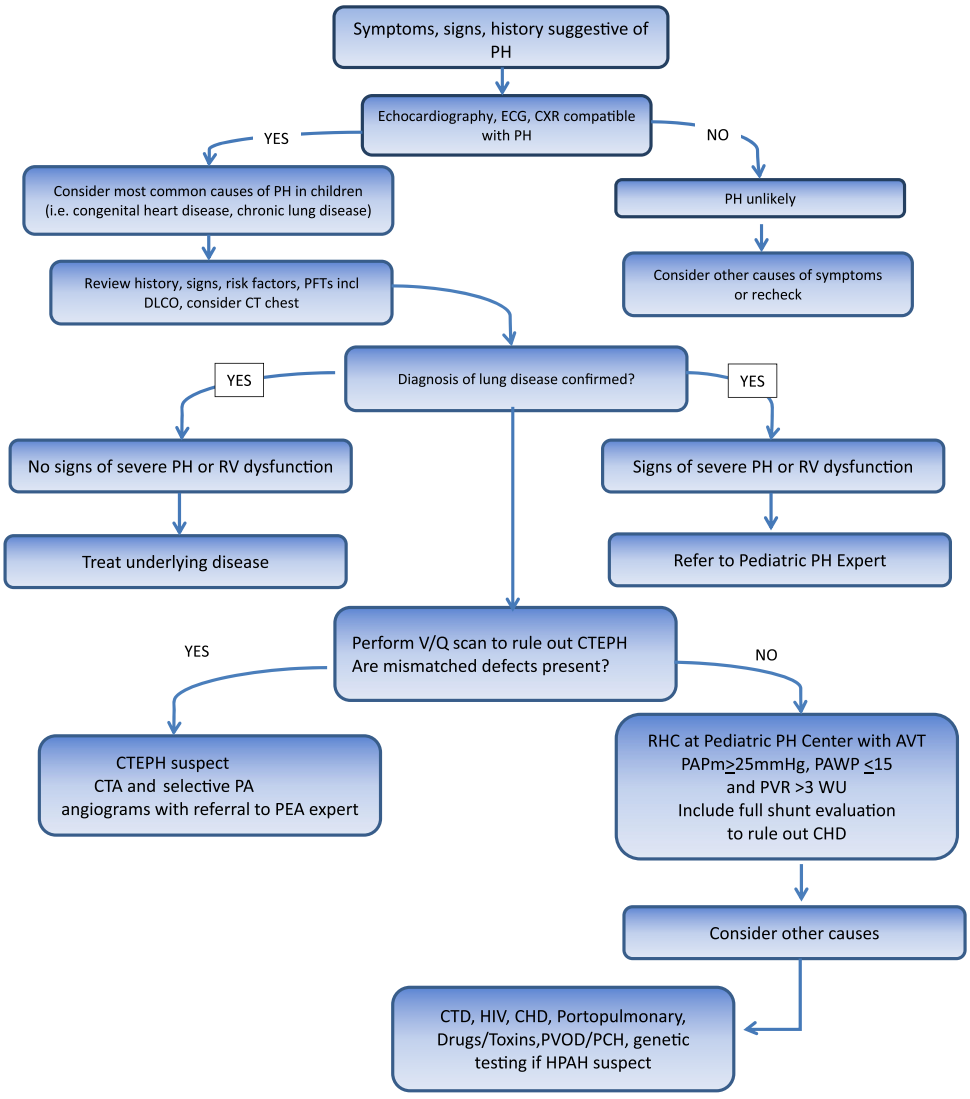

Figure 2 **Pulmonary Arterial Hypertension Diagnostic Work-Up**

#If a reliable test cannot be obtained in a young child and there is a high index of suspicion for underlying lung disease, the patient may require further lung imaging. ¶Children 7 years of age and older can usually perform reliably to assess exercise tolerance and capacity in conjunction with diagnostic work-up. AVT = acute vasodilator testing; CHD = congenital heart disease; CT = computed tomography; CTA = computed tomography angiography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; CXR = chest radiography; DLCO = diffusing capacity of the lung for carbon monoxide; ECG = electrocardiogram; HPAH = heritable pulmonary arterial hypertension; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PCH = pulmonary capillary hemangiomatosis; PEA = pulmonary endarterectomy; PFT = pulmonary function test; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = right ventricular; V/Q = ventilation/perfusion; WU = Wood units.

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

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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 (3,34,36,43), 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 × m^2 (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

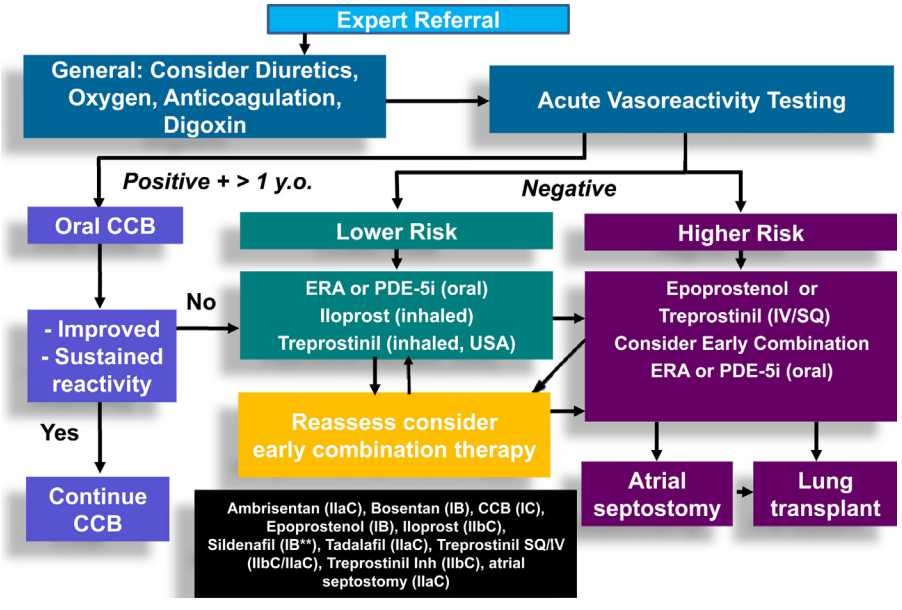

Figure 3 World Symposium on Pulmonary Hypertension 2013 Consensus Pediatric IPAH/FPAH Treatment Algorithm*

*Use of all agents is considered off-label in children aside from sildenafil in Europe. **Dosing recommendations per European approved dosing for children. See text for discussion of use of sildenafil in children in the United States. CCB = calcium channel blocker; ERA = endothelin receptor antagonist; HPAH = hereditary pulmonary arterial hypertension; inh = inhalation; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; PDE-5i = phosphodiesterase 5 inhibitor; SQ = subcutaneous.

treatment strategies. However, the use of targeted pulmonary PAH therapies in children is almost exclusively based on experience and data from adult studies, rather than evidence from clinical trials in pediatric patients. Due to the complex etiology and relative lack of data in children with PAH, selection of appropriate therapies remains difficult. 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 × 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

Table 4 Pediatric Determinants of Risk

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I,II	WHO functional class	III,IV
Minimally elevated	SBNP/NTproBNP	Significantly elevated Rising level
	Echocardiography	Severe RV enlargement/dysfunction Pericardial Effusion
Systemic CI >3.0 l/min/m^2 mPAP/mSAP <0.75 Acute vasoreactivity	Hemodynamics	Systemic CI <2.5 l/min/m^2 mPAP/mSAP >0.75 RAP >10 mm Hg PVRI >20 WU·m^2

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 (l1,12,70,90,93–96) 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.

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REFERENCES

1. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006. Heart 2009;95:312–7.
2. Fraisse A, Jais X, Schleich JM, et al. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. Arch Cardiovasc Dis 2010;103:66–74.
3. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012;125:113–22.
4. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379:537–46.
5. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011;37:665–77.
6. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343–9.
7. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. J Am Coll Cardiol 1999;33:813–9.
8. Rimensberger PC, Spahr-Schopfer I, Berner M, et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation 2001;103:544–8.
9. Balzer DT, Kort HW, Day RW, et al. Inhaled nitric oxide as a preoperative test (INOP test I): the INOP Test Study Group. Circulation 2002;106:I76–81.
10. Ivy DD, Doran AK, Smith KJ, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 2008;51:161–9.
11. Takatsuki S, Parker DK, Doran AK, Friesen RH, Ivy DD. Acute pulmonary vasodilator testing with inhaled treprostinil in children with pulmonary arterial hypertension. Pediatr Cardiol 2013;34:1006–12.
12. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation 2004;110:660–5.
13. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105–11.
14. Giglia TM, Humpl T. Preoperative pulmonary hemodynamics and assessment of operability: is there a pulmonary vascular resistance that precludes cardiac operation? Pediatric Crit Care Med 2010;11:S57–69.
15. Moller JH, Patton C, Varco RL, Lillehei CW. Late results (30 to 35 years) after operative closure of isolated ventricular septal defect from 1954 to 1960. Am J Cardiol 1991;68:1491–7.
16. Douwes JM, van Loon RL, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria. Eur Heart J 2011;32:3137–46.
17. Kawut SM, Horn EM, Berekashvili KK, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol 2005;95:199–203.
18. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43–54.
19. Austin ED, Ma L, LeDuc C, et al. Whole exome sequencing to identify a novel gene (caveolin-1) associated with human pulmonary arterial hypertension. Circ Cardiovasc Genet 2012;5:336–43.
20. Ma L, Roman-Campos D, Austin ED, et al. A novel channelopathy in pulmonary arterial hypertension. N Engl J Med 2013;369:351–61.
21. Kerstjens-Frederikse WS, Bongers EM, Roofthooft MT, et al. TBX4 mutations (small patella syndrome) are associated with childhood-onset pulmonary arterial hypertension. J Med Genet 2013;50:500–6.
22. Adatia I, Kulik T, Mullen M. Pulmonary venous hypertension or pulmonary hypertension due to left heart disease. Prog Pediatr Cardiol 2009;27:35–42.

23. Mourani PM, Abman SH. Pulmonary vascular disease in bronchopulmonary dysplasia: pulmonary hypertension and beyond. Curr Opin Pediatr 2013;25:329–37.
24. Thebaud B, Tibboel D. Pulmonary hypertension associated with congenital diaphragmatic hernia. Cardiol Young 2009;19 Suppl 1: 49–53.
25. Rollins MD. Recent advances in the management of congenital diaphragmatic hernia. Curr Opin Pediatr 2012;24:379–85.
26. Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ 2011;1:286–98.
27. Mitchell MB, Campbell DN, Ivy D, et al. Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. J Thorac Cardiovasc Surg 2004;128:693–702.
28. Takatsuki S, Soep JB, Calderbank M, Ivy DD. Connective tissue disease presenting with signs and symptoms of pulmonary hypertension in children. Pediatr Cardiol 2011;32:828–33.
29. Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down's syndrome. N Engl J Med 1982;307:1170–3.
30. Cua CL, Rogers LK, Chicoine LG, et al. Down syndrome patients with pulmonary hypertension have elevated plasma levels of asymmetric dimethylarginine. Eur J Pediatr 2011;170:859–63.
31. Hawkins A, Langton-Hewer S, Henderson J, Tulloh RM. Management of pulmonary hypertension in Down syndrome. Eur J Pediatr 2011;170:915–21.
32. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation 2011;124:1755–64.
33. Levy M, Celermajer D, Szezepanski I, Boudjemline Y, Bonnet D. Do tertiary paediatric hospitals deal with the same spectrum of paediatric pulmonary hypertension as multicentre registries? Eur Respir J 2013; 41:236–9.
34. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 2010;96:1401–6.
35. Sandoval J, Bauerle O, Gomez A, Palomar A, Martinez Guerra ML, Furuya ME. Primary pulmonary hypertension in children: clinical characterization and survival. J Am Coll Cardiol 1995;25:466–74.
36. van Loon RL, Roofthooft MT, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol 2010;106:117–24.
37. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 2013 Mar 1 [E-pub ahead of print].
38. Haworth SG. The management of pulmonary hypertension in children. Arch Dis Child 2008;93:620–5.
39. Rosenzweig EB, Feinstein JA, Humpl T, Ivy DD. Pulmonary arterial hypertension in children: diagnostic work up and challenges. Prog Pediatr Cardiol 2009;27:7–11.
40. Beghetti M, Berger RM, Schulze-Neick I, et al. Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice. Eur Respir J 2013;42:689–700.
41. Condino AA, Ivy DD, O'Connor JA, et al. Portopulmonary hypertension in pediatric patients. J Pediatr 2005;147:20–6.
42. Lammers AE, Adatia I, Cerro MJ, et al. Functional classification of pulmonary hypertension in children: report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ 2011;1:280–5.
43. Ivy DD, Rosenzweig EB, Lemarie JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. Am J Cardiol 2010;106:1332–8.
44. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, Ivy DD. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest 2009;135:745–51.
45. Lammers AE, Hislop AA, Haworth SG. Prognostic value of B-type natriuretic peptide in children with pulmonary hypertension. Int J Cardiol 2009;135:21–6.
46. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res 2008;63:321–7.
47. Lammers AE, Munnery E, Hislop AA, Haworth SG. Heart rate variability predicts outcome in children with pulmonary arterial hypertension. Int J Cardiol 2010;142:159–65.
48. Carmosino MJ, Friesen RH, Doran A, Ivy DD. Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. Anesth Analg 2007;104: 521–7.
49. Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: current insights from the Magic registry. Catheter Cardiovasc Interv 2010;76:865–73.
50. Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MR. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. Br J Anaesth 2007;98:657–61.
51. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. Am J Cardiol 2010; 106:430–6.
52. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and Doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J 2013;165:1024–31.
53. Lammers AE, Haworth SG, Riley G, Maslin K, Diller GP, Marek J. Value of tissue Doppler echocardiography in children with pulmonary hypertension. J Am Soc Echocardiogr 2012;25:504–10.
54. Takatsuki S, Nakayama T, Jone PN, et al. Tissue Doppler imaging predicts adverse outcome in children with idiopathic pulmonary arterial hypertension. J Pediatr 2012;161:1126–31.
55. Koestenberger M, Ravekes W, Everett AD, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr 2009;22:715–9.
56. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, Haworth SG. Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child 2011;96:141–7.
57. Smith G, Reyes JT, Russell JL, Humpl T. Safety of maximal cardiopulmonary exercise testing in pediatric patients with pulmonary hypertension. Chest 2009;135:1209–14.
58. Moledina S, Pandya B, Bartsota M, et al. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging 2013;6:407–14.
59. Hunter KS, Lee PF, Lanning CJ, et al. Pulmonary vascular input impedance is a combined measure of pulmonary vascular resistance and stiffness and predicts clinical outcomes better than pulmonary vascular resistance alone in pediatric patients with pulmonary hypertension. Am Heart J 2008;155:166–74.
60. Sajan I, Manlhiot C, Reyes J, McCrindle BW, Humpl T, Friedberg MK. Pulmonary arterial capacitance in children with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease: relation to pulmonary vascular resistance, exercise capacity, and survival. Am Heart J 2011;162:562–8.
61. Moledina S, de Bruyn A, Schievano S, et al. Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: a proof of principle study. Heart 2011;97:1245–9.
62. Duncan M, Wagner BD, Murray K, et al. Circulating cytokines and growth factors in pediatric pulmonary hypertension. Mediators Inflamm 2012;2012:143428.
63. Yeager ME, Colvin KL, Everett AD, Stenmark KR, Ivy DD. Plasma proteomics of differential outcome to long-term therapy in children with idiopathic pulmonary arterial hypertension. Proteomics Clin Appl 2012;6:257–67.
64. Smadja DM, Mauge L, Gaussem P, et al. Treprostinil increases the number and angiogenic potential of endothelial progenitor cells in children with pulmonary hypertension. Angiogenesis 2011;14:17–27.
65. Yeager ME, Nguyen CM, Belchenko DD, et al. Circulating myeloid-derived suppressor cells are increased and activated in pulmonary hypertension. Chest 2012;141:944–52.
66. Yeager ME, Nguyen CM, Belchenko DD, et al. Circulating fibrocytes are increased in children and young adults with pulmonary hypertension. Eur Respir J 2012;39:104–11.

67. Cabral JE, Belik J. Persistent pulmonary hypertension of the newborn: recent advances in pathophysiology and treatment. J Pediatr (Rio J) 2013;89:226–42.
68. Lakshminrusimha S. The pulmonary circulation in neonatal respiratory failure. Clin Perinatol 2012;39:655–83.
69. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573–619.
70. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999;99:1197–208.
71. Barst RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. Clin Pharmacol Ther 2003;73:372–82.
72. Beghetti M, Haworth SG, Bonnet D, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. Br J Clin Pharmacol 2009;68:948–55.
73. Beghetti M, Hoeper MM, Kiely DG, et al. Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance Program. Pediatr Res 2008;64:200–4.
74. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114:48–54.
75. Hislop AA, Moledina S, Foster H, Schulze-Neick I, Haworth SG. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J 2011;38:70–7.
76. Maiya S, Hislop AA, Flynn Y, Haworth SG. Response to bosentan in children with pulmonary hypertension. Heart 2006;92:664–70.
77. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol 2005;46:697–704.
78. Takatsuki S, Rosenzweig EB, Zuckerman W, Brady D, Calderbank M, Ivy DD. Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. Pediatr Pulmonol 2013;48:27–34.
79. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol 2011;107:1381–5.
80. Abman SH, Kinsella JP, Rosenzweig EB, et al. Implications of the U.S. Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension. Am J Respir Crit Care Med 2013;187:572–5.
81. Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. Heart 2000;84:E4.
82. Apitz C, Reyes JT, Holtby H, Humpl T, Redington AN. Pharmacokinetic and hemodynamic responses to oral sildenafil during invasive testing in children with pulmonary hypertension. J Am Coll Cardiol 2010;55:1456–62.
83. Barst RJ, Layton GR, Konourina I, Richardson H, Beghetti M, Ivy DD. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive patients with pediatric pulmonary arterial hypertension(abstr). Eur Heart J 2012;33 Suppl 1:979.
84. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation 2012;125:324–34.
85. Humpl T, Reyes JT, Erickson S, Armano R, Holtby H, Adatia I. Sildenafil therapy for neonatal and childhood pulmonary hypertensive vascular disease. Cardiol Young 2011;21:187–93.
86. Humpl T, Reyes JT, Holtby H, Stephens D, Adatia I. Beneficial effect of oral sildenafil therapy on childhood pulmonary arterial hypertension: twelve-month clinical trial of a single-drug, open-label, pilot study. Circulation 2005;111:3274–80.
87. Rosenzweig EB. Tadalafil for the treatment of pulmonary arterial hypertension. Expert Opin Pharmacother 2010;11:127–32.
88. Takatsuki S, Calderbank M, Ivy DD. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. Pediatr Cardiol 2012;33:683–8.
89. Limsuwan A, Wanitkul S, Khosithset A, Attanavanich S, Samankatiwat P. Aerosolized iloprost for postoperative pulmonary hypertensive crisis in children with congenital heart disease. Int J Cardiol 2008;129:333–8.
90. Melnick L, Barst RJ, Rowan CA, Kerstein D, Rosenzweig EB. Effectiveness of transition from intravenous epoprostenol to oral/inhaled targeted pulmonary arterial hypertension therapy in pediatric idiopathic and familial pulmonary arterial hypertension. Am J Cardiol 2010;105:1485–9.
91. Tissot C, Beghetti M. Review of inhaled iloprost for the control of pulmonary artery hypertension in children. Vasc Health Risk Manag 2009;5:325–31.
92. Krishnan U, Takatsuki S, Ivy DD, et al. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. Am J Cardiol 2012;110:1704–9.
93. Ivy DD, Calderbank M, Wagner BD, et al. Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension. Infect Control Hosp Epidemiol 2009;30:823–9.
94. Lammers AE, Hislop AA, Flynn Y, Haworth SG. Epoprostenol treatment in children with severe pulmonary hypertension. Heart 2007;93:739–43.
95. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 1999;99:1858–65.
96. Siehr SL, Ivy DD, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: long-term hemodynamics. J Heart Lung Transplant 2013;32:546–52.
97. Doran AK, Ivy DD, Barst RJ, Hill N, Murali S, Benza RL. Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. Int J Clin Pract Suppl 2008;(160):5–9.
98. Levy M, Celermajer DS, Bourges-Petit E, Del Cerro MJ, Bajolle F, Bonnet D. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. J Pediatr 2011;158:584–8.
99. Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 1998;32:297–304.
100. Baruteau AE, Serraf A, Levy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: long-term results. Ann Thorac Surg 2012;94:817–24.

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