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Current Challenges in Pediatric Pulmonary Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) in the pediatric population is associated with a variety of underlying diseases and causes, significantly morbidity and mortality. In the majority of patients, PAH in children is idiopathic or associated with congenital heart disease (CHD), with pulmonary hypertension (PH) associated with connective tissue disease, a rare cause in children.

Classification of pediatric PH has generally followed the WHO classification, but recognition of the importance of fetal origins of PH and developmental abnormalities have led to the formation of a new pediatric-specific classification. Incidence data from the Netherlands has revealed an annual incidence and point prevalence of 0.7 and 4.4 for idiopathic PAH and 2.2 and 15.6 for associated pulmonary arterial hypertension-CHD cases per million children. Although the treatment with new selective pulmonary vasodilators offers hemodynamic and functional improvement in pediatric populations, the treatments in children largely depend on results from evidence-based adult studies and experience of clinicians treating children. A recent randomized clinical trial of sildenafil and its long-term extension has led to disparate recommendations in the United States and Europe.

Keywords

pulmonary arterial hypertension; congenital heart disease; children; pediatric pulmonary vascular disease

Pulmonary hypertension (PH) can present at any age from infancy to adulthood. The distribution of etiologies in children is quite different from adults with a predominance of idiopathic cases (idiopathic pulmonary arterial hypertension [IPAH]) or associated pulmonary arterial hypertension with congenital heart disease (APAH-CHD).^{1–4} 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 might be worse compared with adults.⁵ Therapeutic strategies for adult PAH have not been sufficiently studied in children, especially regarding potential toxicities or optimal dosing, and appropriate endpoints 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 to PAH in children.

Classification

The most current classification of PH was established at the 4th World Symposium held in 2008 in Dana Point, CA.^{6,7} However, the Dana Point classification does not completely reflect the complexity of pediatric disease, as it does not include the heterogeneity of factors that contribute to pediatric pulmonary hypertensive vascular disease (Fig. 1).^{8–10} PH can develop in utero or can be superimposed on key periods of lung development leading to life-long airway and pulmonary vascular abnormalities. Many children presenting with PH have heterogeneous disease consisting of varying predisposing factors, including prematurity, a chromosomal or genetic anomaly, CHD, and sleep disordered breathing. Therefore, a classification system of pediatric pulmonary hypertensive vascular disease was developed by the Pediatric Taskforce of the Pulmonary Vascular Research Institute at the 2011 Panama meeting (Table 1).⁸ This pediatric classification recognized the concepts of the contribution of abnormalities of lung growth and development to pediatric PH and highlighted multifactorial causes of PH such as CHD, chromosomal anomalies, sleep disorder, chronic aspiration, and prenatal contributions to postnatal lung disease. In particular, this classification recognizes the concepts of the contribution of abnormalities of lung growth and development to pediatric PH. In the new classification, pediatric pulmonary hypertensive vascular diseases are divided into 10 broad categories from the neonate to adolescent. Particularly, the sections of prenatal or developmental pulmonary vascular disease, congenital malformation syndromes, and bronchopulmonary dysplasia are not categorized in the Dana Point Classification as these categories provide different causes from those of adult PH. The Panama classification of pediatric pulmonary hypertensive vascular disease provides a comprehensive classification of almost all causes of pediatric PH.

Definition

The term pulmonary hypertension refers to the presence of abnormally high pulmonary artery pressure greater than 25 mm Hg. The conventional definition of PAH, which is categorized Group 1 in the Dana point classification, includes a mean pulmonary artery pressure of greater than 25 mm Hg, with a normal pulmonary artery occlusion pressure of 15 mm Hg or less.¹¹ Although a specific threshold value for pulmonary vascular resistance (PVR) is currently not included in the definition of adult patients with PAH, the inclusion of an increase in pulmonary vascular resistance index (PVRI) $> 3 \text{ Wood units} \times \text{m}^2$ is important to include in pediatric PAH, particularly in children with CHD. Children with a large unrestrictive ventricular defect have high pulmonary artery pressure with variable flow. In the presence of high pulmonary blood flow and high pulmonary to systemic blood flow ratio, PVRI is low and thus the defect is likely amenable for surgical repair. However, in the presence of pulmonary vascular obstructive disease with high PVRI, pulmonary blood flow is decreased and may lead to right-to-left shunting and an inoperable state (Eisenmenger syndrome).¹² In children with a biventricular circulation, the definition is same as the conventional definition, but the Panama classification includes children with a single ventricle and a cavopulmonary anastomosis.⁸ These children may have elevated PVR after cavopulmonary anastomosis without elevation of pulmonary artery pressure beyond 25 mm Hg, and in fact a pulmonary artery pressure greater than 20 mm Hg is life threatening in these patients. Therefore, pediatric pulmonary hypertensive vascular disease following cavopulmonary anastomosis may be defined as a PVRI $> 3 \text{ Wood units} \times \text{m}^2$ or a transpulmonary gradient $> 6 \text{ mm Hg}$, whereas PAH in biventricular circulations is defined as a mean pulmonary artery pressure $> 25 \text{ mm Hg}$, a pulmonary artery occlusion pressure $< 15 \text{ mm Hg}$, and a PVRI $> 3 \text{ Wood units} \times \text{m}^2$. As children may have a lower blood pressure than adults, PAH may also be described according to the ratio of pulmonary artery systolic

pressure divided by systemic artery systolic pressure with a ratio greater than 0.5, but this definition has not been globally accepted or validated.

Pathogenesis

Pulmonary arterial hypertension (PAH) is characterized by a complex arteriopathy consisting of intimal thickening and fibrosis, medial hypertrophy and hyperplasia, and adventitial change. Alterations in endothelial function are noted before structural changes, and include distal extension of smooth muscle into nonmuscular regions of the vasculature. Important proliferative mediators include increased thromboxane A₂ and endothelin-1, and decreased vasodilator and antiproliferative vasoactive mediators, such as prostacyclin and nitric oxide.^{13–15} Recent interest in stem cells/progenitor cells has enhanced our knowledge of the role of extravascular cells in the development of the fibroproliferative process. Endothelial progenitor cells (EPCs) contribute to vascular repair and new vessel formation.^{16–20} Circulating EPCs are a noninvasive marker of vascular damage, remodeling, and dysfunction.^{16,17} An open-label, non-randomized pilot trial showed that the transplantation of EPCs may improve exercise capacity, functional class, and pulmonary hemodynamics in children with IPAH.²¹ In contrast, mechanisms contributed by inflammatory cells in pediatric PAH have not been thoroughly investigated. Fibrocytes are characterized by expression of CD45 (leukocytes) and collagen and are recruited to sites of injury in persistent inflammatory remodeling and proangiogenic signaling.^{22,23} Fibrocytes are associated with poor prognosis in patients with idiopathic pulmonary fibrosis.²³ Similarly, myeloid-derived suppressor cells (MDSCs) are increased in inflammatory disease and orchestrate immune cell responses. Recent published studies have evaluated circulating fibrocytes and MDSCs in 26 children with PAH compared with non-PAH controls.^{24,25} Circulating fibrocytes and MDSCs in children with PAH were increased compared with controls. Higher numbers of fibrocytes and MDSCs correlated to increasing pulmonary artery pressure, suggesting an inflammatory component to pediatric PAH (Fig. 2).

Etiology

Current registries have begun to explore differences in etiology between adult and pediatric PH. In children, idiopathic PAH, heritable PAH, and PAH associated with CHD are the majority of the causes, while PAH associated with connective tissue disease is a rare cause.^{1–4} In contrast, connective tissue disease is frequent in adult patients with PAH. Large registries of pediatric PH (The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry) are currently being conducted.² In 362 PAH patients with confirmed PAH in this registry, 88% had PAH, which was characterized as IPAH or FPAH in 182 (57%) or associated with CHD in 115. Forty-two patients (12%) had PH associated with respiratory disease or hypoxemia, with bronchopulmonary dysplasia the most frequent. Only three patients had either chronic thromboembolic PH or miscellaneous causes of PH. Chromosomal anomalies, mainly trisomy 21, were reported in 47 (13%) patients with confirmed disease. Another large registry for pediatric PH has been reported from the nationwide Netherlands PH service.²⁶ In this registry, 2,845 of 3,263 pediatric patients with PH had PAH (Dana point Group 1), including transient PAH (82%), progressive PAH (5%), or PH crisis (1%). The remaining causes of PH included lung disease and/or hypoxemia (8%), PH included with left heart disease (5%), and chronic thromboembolic PH (< 1%). The most common causes of transient PH were persistent pulmonary hypertension of the neonate (PPHN) (58%) and PAH associated with CHD (42%) which resolved after surgical repair. PAH associated with CHD (72%) and idiopathic PAH (23%) were common causes among the progressive PAH cases. Down syndrome was the most frequent chromosomal disorder (12%) as was seen in the result of *TOPP* registry.

Epidemiology and Survival

Although the exact incidence and prevalence of PH in pediatric population is 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 (Fig. 3). The annual incidence rates of idiopathic PAH and PAH associated with CHD were 0.7 and 2.2 cases per million, respectively. The point prevalence of PAH associated with 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.²⁶ Likewise, the incidence of idiopathic PAH 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.²⁷ In the French registry, the estimated prevalence for chronic PAH was 3.7 cases/million.⁴

Without appropriate treatments, median survival rate after diagnosis of children with IPAH might be worse compared with adults, and was 10 months for children in the NIH registry of patients with IPAH.⁵ In 1995, before the availability of targeted PAH therapies, a single center cohort study showed the estimated median survival of children and adults with idiopathic PAH were similar (4.12 years vs. 3.12 years, respectively).²⁸ Currently, with targeted pulmonary vasodilators, the survival rate has continued to improve in pediatric patients with PAH. Children in the combined adult and pediatric U.S. REVEAL registry (Registry to EValuate EARly and Long-term PAH disease management) demonstrated 1-, 3-, and 5-year estimated survival rates from diagnostic catheterization of $96 \pm 4\%$, $84 \pm 5\%$, and $74 \pm 6\%$, respectively (Fig. 4).¹ There was no significant difference in 5-year survival between idiopathic PAH/familial PAH ($75 \pm 7\%$) and PAH associated with CHD ($71 \pm 13\%$). Additionally, a retrospective study from the UK Pulmonary Hypertension Service for Children has shown the 5-year survival in 216 children with idiopathic PAH and associated PAH.³ The survival rates of idiopathic PAH were 85.6, 79.9, and 71.9% at 1, 3, and 5 years, respectively, whereas associated PAH survival rates were 92.3, 83.8, and 56.9% at 1, 3, and 5 years, respectively (Fig. 5a). In a separate report of idiopathic PAH from the United Kingdom, survival at 1, 3, and 5 years was 89, 84, and 75%, while transplant-free survival was 89, 76, and 57%.²⁷ Reports from the Netherlands have shown worse survival for patients with progressive PAH (not including PPHN or PAH resolving after repair of CHD) with 1-, 3-, and 5-year survival of 73, 63, and 60%, respectively.²⁶ Children with repaired CHD may have worse outcome than other forms of PH (Fig. 5b).³

Clinical Symptoms

Establishing the diagnosis of PAH in the pediatric population still remains difficult because their presentation is often nonspecific. In idiopathic PAH, infants often present with poor appetite, failure to thrive, tachypnea, and irritability due to low cardiac output. Older children present with similar symptoms as adults and complain of exercise intolerance such as dyspnea on exercise, and occasionally chest pain. The most frequent initial presenting symptom in idiopathic PAH and PAH associated with CHD is dyspnea on exertion.^{1,2} The *TOPP* registry has demonstrated that near-syncope and syncope are more common in children with idiopathic PAH and familial PAH,² while peripheral edema is more frequent in adults. Likewise, in the *REVEAL* study, near-syncope or syncope was more frequent in idiopathic PAH and familial PAH patients compared with PAH associated with CHD patients.¹ In idiopathic PAH or PAH associated with repaired CHD, hypoxic seizures may occur, thus children are sometimes misdiagnosed with a seizure disorder.

Treatment and Survival Markers

The traditional clinical endpoints used in adults include World Health Organization (WHO) functional class and 6-minute walk distance. WHO functional class and 6-minute walk distance have been used for predicting survival in adult patients with PAH. However, these endpoints are usually difficult to assess in infants and younger children. However, 6-minute walk test is not reliable in children younger than 5 to 6 years and may not be reproducible in children. The conventional functional classification is difficult to assess in children because their age, physical growth, and maturation influence the functional status. A new functional classification for children with PH has been currently proposed (Table 2).²⁹ This modified classification for children of all ages may be helpful in decision making of treatment strategies in clinical setting.

Many pediatric studies have defined predictive factors associated with worse outcomes. Older age at diagnosis, lower height and weight z-score, and worse WHO functional class predict worse outcome.^{1,27,30} Postoperative CHD with severe PH has a very poor outcome.^{3,26,30} Furthermore, children with Eisenmenger syndrome may have a worse prognosis than patients with Eisenmenger syndrome surviving to adulthood.²⁶

Recent published studies have also demonstrated that circulating biomarkers, echocardiographic data, and hemodynamics may have predictive value for prognosis in children with PH. The measurement of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NTproBNP) have shown clinical utility in the decision-making process in children with PAH.^{31–34} The *REVEAL* study suggested that low BNP (< 50 pg/mL) or NTproBNP (< 300 pg/mL) has utility as a prognostic parameter for decreased mortality in children with PAH.¹ Conversely, plasma BNP > 130 to 180 pg/mL or serum NTproBNP level of > 605 to 1,400 pg/mL identifies pediatric patients with poor long-term prognosis.^{31,32,34} A recent pediatric study has shown a strong correlation between BNP and NTproBNP levels and both biomarkers may be equally useful for evaluating disease severity, although due to different half-lives, one may be more appropriate in a certain context.³⁵ On the average, a 1-unit increase in log BNP or NTproBNP was associated with 4.5 units $\times$ m² or 3.4 units $\times$ m² increase in PVRI, respectively.³³ In sickle cell disease, NTproBNP correlated with low hemoglobin and tissue Doppler data as indicators of diastolic dysfunction.³⁵ It is important to consider that BNP and NTproBNP levels change with age and gender in children. Other biomarkers, such uric acid are also predictors of poor survival.³⁴

A proteomic approach has been applied to pediatric PAH. Using nonbiased gel-based proteomic analysis, differences in plasma proteins known to modulate inflammation have been found between children with a good or poor outcome to chronic therapy.³⁶ Before and after therapy, serum amyloid A-4 was fourfold higher in those with poor outcome (death, initiation of intravenous prostacyclin) compared with those with good outcome (survival, discontinuation of intravenous prostacyclin) (Fig. 6).³⁶

Echocardiography provides both anatomical and functional information in a noninvasive setting. Several clinical studies have shown useful echocardiographic parameters for predicting disease severity and survival in adults with PAH, including tricuspid annular plane systolic excursion,³⁷ myocardial performance index,³⁸ and right ventricular diastolic/systolic velocities evaluated by tissue Doppler imaging (TDI).^{35,39–41} In recent pediatric studies, right ventricular TDI velocity was lower in children with PAH compared with healthy controls.^{39,41} Moreover, tricuspid diastolic velocity (E') had significant inverse correlations with right ventricular end-diastolic pressure and mean pulmonary arterial pressure.⁴¹ Statistically significant differences were observed in tricuspid E' velocity

between New York Heart Association (NYHA) functional class II and combined III and IV. Cumulative event-free survival rate was significantly lower when tricuspid E' velocity was 8 cm/s (log-rank test, $p < 0.001$) (Fig. 7).⁴¹ The systolic-to-diastolic duration ratio (S:D ratio) (Fig. 8) was evaluated in 503 serial echocardiograms in 47 children with PAH and 47 age-matched controls. The S:D ratio was significantly higher in patients than in controls (1.38 ± 0.61 vs. 0.72 ± 0.16 , $p < 0.001$). A higher S:D ratio was associated with worse echocardiographic RV fractional area of change, worse catheterization hemodynamics, shorter 6-minute walk distance, and worse clinical outcomes independent of pulmonary resistance or pressures. An increase of 0.1 in the S:D ratio was associated with a 13% increase in yearly risk for lung transplantation or death (hazard ratio 1.13, $p < 0.001$). An S:D ratio 1.00 to 1.40 was associated with a moderate risk and an S:D ratio > 1.40 was associated with a high risk of a negative outcome.⁴²

Although noninvasive tests are useful in PAH, cardiac catheterization still remains the gold standard for evaluating the disease severity and treatment responses in children. Hemodynamic parameters have been shown to correlate with prognosis in children; elevated right atrial pressure > 10 mm Hg, low cardiac index < 2.1 L/min/m² and low central venous oxygen saturation $< 64\%$ are identified in patients at higher risk of death.^{1,30} Acute vasodilator testing is essential to determine initial therapy in children, but additional information can be obtained from repeat vasoreactivity testing. Children who maintain vasoreactivity at repeat cardiac catheterization may have a better prognosis.^{1,43} High baseline mPAP/mSAP and PVR/SVR is associated with worse prognosis independent from age, diagnosis, or the presence of a post-tricuspid shunt.⁴³

Currently, total compliance of the pulmonary vascular bed, defined as the ratio of stroke volume (SV) and pulmonary artery pulse pressure (PP), has been evaluated for predicting survival in PAH patients.^{44–52} This novel index (pulmonary arterial capacitance, PAC) is an indicator of the workload on the right ventricle. The compliance of pulmonary artery measures how much the pulmonary vasculature will dilate with each contraction of the right ventricle. PAC/PAC_i can be calculated as follows: $PAC = \Delta volume / \Delta pressure = SV(mL) / PP(mm\ Hg)$; $PAC_i = (SV/BSA) / PP$. A $PAC_i < 0.70$ mL/mm Hg per square meter or > 1.25 mL/mm Hg per square meter and a $PVR_i > 13$ Wood units $\times m(2)$ are associated with decreased freedom from death or lung transplant.⁵¹ Impedance, a measure of PVR and pulmonary vascular stiffness, has also been evaluated and may be a better predictor of outcome than PVR alone.⁵³

Evaluation

Because of the many diseases associated with PH, a methodical and comprehensive evaluation is important. The most successful strategy in treatment of PH is correction of an underlying abnormality, rather than addition of vasodilator therapy. A diagnostic algorithm is shown in Fig. 9.⁵⁴ Special situations may predispose to the development of PAH. As an example, children living at altitude and presenting with high-altitude pulmonary edema should be screened for PH.⁵⁵ In addition, children with biliary atresia, cavernous transformation of the portal vein, primary sclerosing cholangitis, or cryptogenic cirrhosis may have portopulmonary hypertension with an associated high mortality.^{56,57}

Vasodilator Therapies

The prognosis of children with PAH has improved in the past decade owing to new therapeutic agents. Use of targeted pulmonary vasodilators in children is almost exclusively based on experience rather than evidence from clinical trials. Because of the complex etiology and relative lack of data in children with PAH, selection of appropriate therapies

remains difficult. A treatment algorithm in children with severe PAH has been proposed (Fig. 10).⁵⁸ As shown, calcium channel blockers may be used in responders to acute vasodilator testing, but most children will require other forms of therapy. Vasoreactivity testing for treatment of PAH is very different from determination of suitability for repair of congenital cardiac lesions. The description below only applies to the use of vasodilators in patients with PAH for long-term therapy. Douwes et al evaluated the occurrence and prognostic value of an acute vasodilator response in pediatric patients with idiopathic PAH/heritable PAH and PAH associated with CHD for long-term therapy.⁴³ The Barst criteria (decrease in mPAP of $\geq 20\%$, unchanged or increased cardiac index, and decreased or unchanged pulmonary to systemic vascular resistance ratio (PVR/SVR), Rich criteria (decrease in mPAP and PVR of $\geq 20\%$), and Sitbon criteria (decrease in mPAP of ≥ 10 mm Hg reaching a mPAP value of ≤ 40 mm Hg and an increased or unchanged cardiac output) were compared (Fig. 11). The proportion of patients with acute vasoreactivity highly depends on the used criteria, but did not differ between pediatric and adult IPAH/HPAH. No responders were identified in patients with a posttricuspid shunt. Similar to the *REVEAL* study, the number of responders in idiopathic PAH/heritable PAH was higher than those in PAH associated with CHD, and maintenance of an acute vasodilator response during follow-up was associated with better survival.^{1,43}

In contrast, nonresponders to acute vasodilator testing with right heart failure should consider continuous prostacyclin therapy, while other oral medications are first-line therapy in the nonresponders without right heart failure. Unfortunately, there are limited data of treatment strategies in children with PH due to few randomized controlled clinical trials evaluating the safety and efficacy of specific treatments.

Prostacyclins

Epoprostenol has been used for over two decades for the treatment of PAH with great success.^{3,59–67} Epoprostenol is recommended for first-line treatment of PAH patients with NYHA functional class III–IV symptoms.^{7,58} Clinical effects occur with long-term use even in patients without a response during vasodilator testing. Although epoprostenol is not approved in children, continuous intravenous epoprostenol therapy is effective for improving symptoms, hemodynamics, and survival in children with idiopathic PAH or PAH associated with CHD.^{60,63–68} Barst et al have shown improved survival in children treated with long-term intravenous epoprostenol, with a 5-year survival rate for treated children of 81%⁶⁰ (Fig. 12), while Yung et al have reported a 10-year treatment success rate (freedom from death, transplantation, or atrial septostomy) of 37%.⁶⁷ Experience in the United Kingdom has shown cumulative survival on epoprostenol at 1, 2, and 3 years of 94, 90, and 84%. In children on intravenous epoprostenol, weight improved significantly from a baseline z score of -1.55 (1.74) to -1.16 (1.8) ($p < 0.03$).⁶⁵

Treprostinil shares the same pharmacologic actions as epoprostenol and may be used as treatment via three different routes of administration: subcutaneous, intravenous, and inhaled. Treprostinil has stability at room temperature, smaller pump options, and longer half-life as compared with epoprostenol, which are seen as advantages. Recent studies have shown favorable experiences of switching from epoprostenol to intravenous treprostinil therapy in children.^{63,68–70} Despite higher doses, overall side effects, with the exception of leg pain, were lower with intravenous treprostinil.⁶³ Continuous infusion of prostacyclin through a central venous catheter increases the risk of catheter-related blood stream infections. The risk of gram-negative infection with intravenous treprostinil led to evaluation by many centers of possible mechanisms.⁷¹ Use of closed hub systems with protection of catheter connections while showering decreased the risk of gram-negative infections in children on intravenous treprostinil.^{72,73} Further, use of the diluent for epoprostenol with

intravenous treprostinil to increase the pH of the solution may decrease the risk of infection as well.⁷⁴ Subcutaneous treprostinil offers the advantage of no central venous catheter and has been evaluated in children.⁷⁵ In the European study, eight children received subcutaneous treprostinil therapy after failure of combined oral treatment or because of severe complications with intravenous epoprostenol. Seven patients had significant improvement in functional class, hemodynamics, and 6-minute walk distance. Although injection site pain due to subcutaneous infusion may be a major disadvantage, subcutaneous treprostinil may be tolerated in some children.⁷⁵ Inhaled treprostinil may be used as add-on therapy or used for patients who have injection site pain due to subcutaneous infusion.^{76–78}

Iloprost, an inhaled prostacyclin analog, has several advantages over intravenous epoprostenol infusion therapy including less risk of systemic hypotension and minimizing the effect on ventilation-perfusion mismatch.^{68,79–84} In previous pediatric studies, iloprost improved hemodynamics and WHO functional class in idiopathic PAH and PAH associated with CHD.^{81,83} Moreover, aerosolized iloprost has similar hemodynamic effects given acutely during cardiac catheterization.^{81,85} Because of a short biologic half-life, aerosolized iloprost may be an alternative to inhaled nitric oxide (NO) for vasodilator reactivity testing. In the outpatient setting iloprost therapy requires six to nine inhalations daily, which may limit use in children. Likewise, side effects, such as lower airways reactivity, may also limit its use in children.⁸¹

Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors have been used for over a decade in the treatment of children with PH. PDE-5 inhibitors have antiproliferative, proapoptotic, and vasodilating effects in pulmonary vasculature through an increase in cyclic guanosine monophosphate.^{86,87} PDE-5 inhibitors, such as sildenafil and tadalafil, have been approved for PAH in adult patients.^{88,89} These PDE-5 inhibitors are administered orally and are well tolerated compared with intravenous agents owing to lack of systemic side effects. Sildenafil may also be useful in the setting of inhaled NO therapy withdrawal,^{90–92} in postoperative PH,⁹³ in the presence of PH related to chronic lung disease,⁹⁴ or in single ventricle physiology with high PVR.^{95–107} Sildenafil was initially studied in the outpatient setting in 14 children with PAH. During sildenafil therapy, the mean 6MWT distance increased from 278 ± 114 to 443 ± 107 m over 6 months ($p = 0.02$), and at 12 months, the distance walked was 432 ± 156 m ($p = 0.005$). A plateau was reached between 6 and 12 months ($p = 0.48$). Mean PAP and PVR fell.¹⁰⁸ In children with IPAH and PH associated with CHD, sildenafil improved oxyhemoglobin saturation and exercise capacity without significant side effects.¹⁰⁹ In children with PAH associated with chronic lung disease, sildenafil has been shown to improve hemodynamics in 88% of patients, was well tolerated and did not worsen oxyhemoglobin saturation.¹¹⁰ A study of sildenafil in Japanese children has also suggested safety and efficacy.¹¹¹

The *STARTS-1 trial* was a worldwide randomized, double blind placebo-controlled study of treatment naïve children. In this 16-week, randomized (stratified by weight and ability to exercise), double-blind study the effects of oral sildenafil monotherapy in pediatric PAH were studied.¹¹² Children ($n = 235$) with PAH (aged 1–17 years; ≥ 8 kg) received low (10 mg), medium (10–40 mg), and high (20–80 mg) dose sildenafil or placebo orally three times daily (Table 3). The primary comparison was percent change in peak oxygen consumption (pVO_2) for the three sildenafil doses combined from baseline to week 16; exercise testing was performed only in children able to exercise reliably. Secondary endpoints, including mean PAP, PVR and functional class, were assessed in all enrolled patients, including those unable to reliably exercise. The estimated mean $\pm$ standard error percentage change in pVO_2 for the low-, medium- and high-doses combined versus placebo was $7.7\% \pm 4.0\%$ (95% CI,

−0.2% to 15.6%; $p = 0.056$). Thus, the pre-specified primary outcome measure was not statistically significant (Fig. 13). Peak VO_2 improved only with the medium dose. Secondary outcomes showed a varied response to sildenafil. Functional capacity only improved with high dose sildenafil. While mean PAP improved only with high dose sildenafil, PVRI was lower in children with medium and high dose sildenafil. Upper respiratory tract infections, pyrexia, and vomiting occurred more often with sildenafil than placebo.¹¹²

In the STARTS-2 extension study, children remained on the dose of sildenafil received during STARTS-1.¹¹³ Children receiving placebo were randomized to low, medium or high dose. Subjects were blinded to dose until the STARTS-1 study ended in 2008. Importantly children could be up-titrated on sildenafil by the treating physician and the dose of sildenafil was also increased for weight gain. Importantly, increased mortality was reported in patients randomized to high dose sildenafil monotherapy at 3-years when compared with the lower dose groups. As of August 2011, 37 deaths occurred during the extension phase: 26 patients died while still on therapy and 11 were off treatment. Deaths appeared to be dose-related, with 3-year K-M survival of rates of 94, 93, and 88% (Fig. 14). Hazard ratios for mortality were 3.50 (95% CI, 1.29–9.51) for high versus low dose sildenafil. Review of this data by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) resulted in disparate recommendations. Sildenafil was approved by the European Medicines Agency in 2011, with a later warning on avoidance of use of the high dose. In August 2012, the FDA recently released a strong warning against the (chronic) use of sildenafil for pediatric patients (ages 1 through 17) with PAH. (<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm317743.htm>). The FDA warning states that “...this recommendation against (sildenafil) use is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of Revatio had a higher risk of death than children taking a low dose and (2) the low doses of Revatio are not effective in improving exercise ability. Revatio has never been approved for the treatment of PAH in children, and in light of the new clinical trial information, off-label (not approved by FDA) use of the drug in pediatric patients is not recommended...” Difficulties in interpretation of the STARTS-2 trial arise as (1) There was no placebo group in the STARTS-2 trial; (2) Doses of sildenafil changed during the STARTS-2 trial; (3) Patients requiring additional PAH therapy were withdrawn from STARTS-2; (4) Children were not censored once withdrawn from the study to add therapy or because of withdrawal of consent, but continued to be followed. Follow-up medical treatment after withdrawal is not known and was not standardized, but children were analyzed based on initial randomized dose; (5) Combination therapy was not allowed in the trial; (6) Treatment is not known after withdrawal from the trial in 9/35 deaths; (7) Most patients lost to follow-up were in the high dose group.

Intravenous sildenafil has been studied in children with PPHN and in postoperative CHD. In an open-label, dose-escalation trial in newborns with PPHN and an oxygenation index (OI) > 15, intravenous sildenafil improved oxygenation index compared with placebo in infants with severe PPHN.¹¹⁴ A double blind, multicenter, placebo controlled study of intravenous sildenafil in children with CHD and postoperative PH showed favorable results such as shorter time to extubation and intensive care unit stay, although the study was stopped early due to poor enrollment.¹¹⁵

Tadalafil, a long-acting PDE-5 inhibitor, is a once-daily dosing drug, and has been shown to improve exercise capacity and quality of life measures while reducing clinical worsening in adults.⁸⁸ Although little is known of the use tadalafil in children with PAH, a recent retrospective study suggested clinical efficacy and safety in children with PAH.¹¹⁶ In this open-label study, most patients who switched from sildenafil to tadalafil successfully

continued tadalafil therapy without the need to switch back to sildenafil. Side effect profiles were similar to sildenafil in patients who had transitioned to tadalafil. Furthermore, tadalafil statistically improved hemodynamic data, including mean pulmonary arterial pressure and PVRI compared with sildenafil (Fig. 15).¹¹⁶ An extemporaneously prepared suspension of tadalafil 5 mg/mL has been shown to be stable for at least 91 days when stored in amber plastic bottles at room temperature.¹¹⁷ A FDA panel voted unanimously in favor of use of riociguat, a soluble guanylate cyclase stimulator for PAH as well as chronic thromboembolic pulmonary hypertension in August 2013.

Endothelin Receptor Antagonists

Another target for treatment of PH is the vasoconstrictor peptide endothelin. Bosentan, an oral dual endothelin receptor antagonist, is approved in adult patients with PAH.¹¹⁸ Although oral bosentan in pediatric patients with PAH has been studied, bosentan is not approved in pediatric populations in the United States. In Europe a pediatric formulation is approved by the EMA. Several pediatric studies have demonstrated clinical utility of bosentan therapy, including improvement of exercise capacity, functional class, and long-term outcomes in children with idiopathic PAH and PAH associated with CHD.^{3,27,64,70,119–130} The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was a 16-week, multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of bosentan on systemic pulse oximetry (primary safety end point) and PVR (primary efficacy end point) in patients with WHO functional class III Eisenmenger syndrome. Fifty-four patients were randomized 2:1 to bosentan ($n = 37$) or placebo ($n = 17$) for 16 weeks. The placebo-corrected effect on systemic pulse oximetry was 1.0% (95% confidence interval, -0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced PVRI (-472.0 dyn/s/cm⁵; $p = 0.0383$). Exercise capacity increased (53.1 m; $p = 0.0079$). Bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation.¹³¹ In children, a retrospective, observational study from the United Kingdom in 101 children with idiopathic PAH and PAH associated with CHD showed improvement in WHO functional class and 6-minute walk distance with bosentan; the Kaplan-Meier survival estimates for the 101 patients were 96, 89, 83, and 60% at 1, 2, 3, and 5 years., respectively.¹²⁵ Likewise, in a retrospective cohort study from the United States, 86 consecutive children with idiopathic/heritable or associated PAH, treated with bosentan had a 4 year Kaplan-Meier survival estimate of 82% and Kaplan-Meier estimate of disease progression of 54%.⁷⁰ Bosentan has the potential risk of dose-dependent increases in amino transaminase levels, but these risks are lower in children than adults. A post-marketing survey found elevated aminotransferases in 2.7% of children less than 12 years versus 7.8% of patients over 12 years.¹²² Although the incidence of serum aminotransferase elevation due to bosentan therapy is low in children, liver function tests should be monitored monthly. The BREATHE-3 and FUTURE-1 trials have demonstrated the pharmacokinetics of bosentan with multiple dosages twice daily in pediatric patients with PAH.^{120,132} In the FUTURE-1 trial, bosentan concentrations following doses of 2 and 4 mg/kg were similar, and were lower than adult exposure.¹³² Additional studies are underway to evaluate twice a day versus three times a day dosing.

Ambrisentan is an oral endothelin receptor antagonist and has high selectivity for the endothelin type A receptor. The clinical trials demonstrated the efficacy and safety of ambrisentan through improvements in exercise tolerance, and WHO functional class in adult patients.^{133–136} However, the clinical efficacy and safety of ambrisentan therapy has been not well studied in children with PAH. A recent retrospective study suggested clinical efficacy and safety of ambrisentan in children with PAH.^{137,138} Ambrisentan therapy allowed most children to be successfully switched from bosentan to ambrisentan. In

addition, ambrisentan therapy improved pulmonary artery pressure and WHO functional class in 31% of patients with no elevation of aminotransferase levels (Fig. 16).¹³⁷ Ambrisentan therapy for the pediatric patients requires a larger, controlled study to determine the safety and clinical efficacy.

Combination Therapy

Combination therapy is an attractive option to address simultaneously the multiple pathophysiological pathways present in PAH. It is understandable that acting on the three different pathways of PAH may be more efficacious than acting on a single one, by additive or synergistic effects. In adult patients with PAH, the initiation of combination therapy with epoprostenol and bosentan trended for a greater improvement in hemodynamics when compared with the initiation of epoprostenol alone.¹³⁹ In a randomized placebo controlled trial of initiating sildenafil or placebo to epoprostenol, the addition of sildenafil to long-term intravenous epoprostenol therapy improved exercise capacity, hemodynamic measurements, time to clinical worsening, and quality of life.¹⁴⁰ A therapeutic approach utilizing the combination of bosentan, sildenafil and inhaled iloprost, by acting on the three pathways, has been shown to improve survival, and reduce the need for lung transplantation in adult patients with severe PAH.¹⁴¹ Whether combination therapy should be used as a first step by simultaneous initiation of two or more drugs or by addition of a second treatment to a previous therapy considered insufficient is still not known, and more studies are needed to help establishing guidelines. In the REVEAL registry, most patients received combination therapy for pediatric PAH.¹

Transplantation

Although advances in drug treatment have improved survival of children with PAH over the past two decades, PAH remains a fatal disease and transplantation is an important treatment option for these patients. Transplantation for PAH includes heart-lung transplantation and isolated lung transplantation (usually bilateral). Transplantation options are limited in children due to the availability of suitable donors and limited centers where procedures are available. Furthermore, there are the long-term problems including rejection, infection and other complications of immunosuppression after heart-lung or lung transplantation in children, which are similar to adults. Both single- and bilateral-lung transplantation have been performed in pediatric patients with pulmonary vascular disease and severe right ventricular failure.^{142–146} A report based on a multicenter experience of for pediatric idiopathic PAH with heart-lung or bilateral-lung transplantation has shown the median survival for children in this cohort was 45 months (2–123 months).¹⁴⁴ Similarly, a US cohort of IPAH patients had a median survival for those transplanted of 5.8 years, with 1- and 5-year survival rates of 95 and 61%.¹⁴⁵ Thus, transplantation is a therapeutic option for children with end-stage PAH. The results are not as good as for other solid organ transplants, but are similar to lung transplantation for other reasons. Therefore, transplantation should be reserved for patients with WHO functional class IV, who have progressed despite maximal medical therapy.

Conclusion

The clinical manifestations of pulmonary vascular disease in children differ from adult patients. The diagnosis and assessment of the disease severity are difficult in children with PAH because the traditional adult endpoints such as 6-minute walk distance and WHO functional class are difficult to assess. Recent treatment strategies in children have improved their prognosis dramatically over the past decade since the introduction of new therapeutic agents. Most vasodilator therapies in children are based on experience or expert opinion,

whereas the therapies in adults are evidence based from randomized trials. Managements of pediatric PAH patients are still challenging in current era. Future studies are required for development of specific treatment strategies and clinical endpoints for children with PH.

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Fig. 1.
Heterogeneity and multifactorial elements in pediatric pulmonary hypertensive vascular disease. (Adapted from del Cerro et al.⁸)

Fig. 2. Circulating fibrocytes and myeloid derived suppressor cells in children with PAH compared with non-PAH controls. Fibrocytes in PAH increased in peripheral blood compared with controls ($n = 26$, mean 4.24% versus $n = 10$, mean 0.97%, left), and myeloid derived suppressor cells in PAH increased in peripheral blood compared with controls ($n = 10$ mean 1.86% vs. $n = 10$ mean 0.57%, right). MDSCs: myeloid derived suppressor cells. (Adapted from Yeager et al.^{24,25})

Fig. 3. Annual incidence rates for pediatric pulmonary hypertension in the Netherlands. PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart defects; iPAH, idiopathic PAH. (Adapted from Van Loon et al.²⁶)

Fig. 4.

Five-year survival from diagnostic right heart catheterization (RHC) for all patients diagnosed with pulmonary arterial hypertension during childhood and enrolled in the Registry to Evaluate Early and Long-Term PAH Disease Management within 5 years of diagnostic RHC. ($n = 120$; $74 \pm 6\%$). Data points are survival estimates $\pm$ SE at 1, 3, and 5 years accounting for left truncation. (Adapted from Barst et al.¹)

Fig. 5.

(A) Survival curves for idiopathic pulmonary arterial hypertension (IPAH) and associated pulmonary arterial hypertension (APAH) cases censored for time in the study and for transplantation. There was no significant difference between the two groups. (B) Survival curves for the subgroups within the APAH group. The number in each group (brackets) and the predicted survival out of a possible 5 years are shown. (Adapted from Haworth et al.³)

Fig. 6. Proteomic analysis of long-term outcome response to vasodilator therapy. Before and after therapy, serum amyloid A is significantly higher in non-responders than responders. (Adapted from Yeager et al.³⁶)

Fig. 7. Kaplan-Meier curve. Early diastolic myocardial relaxation velocity (E_m , E') of the tricuspid inflow <8 cm/s was associated with time until an adverse outcome in 35 children with idiopathic PAH. After 12 months, the adverse event rate in the patients classified in the <8 cm/s group was 39% compared with 13% in the >8 cm/s group. (Adapted from Takatsuki et al.⁴¹)

Fig. 8.

In children with PAH, an increased Systolic: Diastolic duration ratio (S:D) of the tricuspid valve is temporally associated with worse RV function, hemodynamics, and exercise capability. The longer S:D duration in the patient on the left (S:D 3.4) was associated with RV failure whereas the patient on the right did not have clinical heart failure (S:D 0.9) despite a similar elevation in tricuspid regurgitation velocity.

Fig. 9.

Pediatric pulmonary arterial hypertension diagnostic work-up. CXR, chest radiography; PH, pulmonary hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; CT, computed tomography. #, if unable to obtain a reliable test 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 can usually perform reliably to assess exercise tolerance and capacity in conjunction with diagnostic workup. (Adapted from Rosenzweig et al.⁵⁷)

Fig. 10.

Treatment algorithm in children with severe pulmonary arterial hypertension. (Adapted from Tissot et al.⁵⁸)

Fig. 11.

The number of acute pulmonary vasodilator responders according to the three criteria in use, in children versus adults with IPAH/HPAH, IPAH/HPAH versus PAH associated with CHD, and patients without versus with post-tricuspid shunt, respectively. These criteria are used to determine long-term therapy and not suitability for repair of congenital heart lesions. There were 14 (Barst criteria; 20%), 20 (Rich criteria; 29%) and 8 (Sitbon criteria; 11%) acute responders in the IPAH/HPAH group, whereas there was one responder (11%) in the CHD group. CHD: congenital heart disease; HPAH: heritable pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; mPAP; mean pulmonary artery pressure; PAH: pulmonary arterial hypertension. (Adapted from Douwes et al.⁴³)

Fig. 12. Kaplan-Meier curves for survival and treatment success in children with IPAH who received epoprostenol ($n = 35$). Survival rates at 1, 3, 5, and 10 years were 94, 88, 81, and 61%, respectively; treatment success rates at 1, 3, 5, and 10 years were 83, 66, 57, and 37%, respectively. (Adapted from Yung et al.⁶⁷)

Fig. 13.

Peak oxygen uptake (% change from baseline to Week 16) in three different dose regimens of sildenafil comparison with placebo ($n = 29$). At week 16, mean peak oxygen uptake (VO_2) was 18.4, 20.4, and 19.0 mL/kg/min for the low-, medium-, and high-dose groups, respectively, versus baseline values of 17.4, 18.0, and 17.4 mL/kg/min. Placebo mean peak VO_2 was 20.0 mL/kg/min at baseline and at week 16. The placebo-corrected estimated mean $\pm$ standard error percent change in peak VO_2 from baseline to end of treatment for the low-, medium-, and high-dose groups combined was $7.7 \pm 4.0\%$ (95% CI, -0.2% to 15.6% ; $p = 0.056$). (Adapted from Barst et al.¹¹²)

Fig. 14. Kaplan-Meier Estimated Survival from Start of Sildenafil Treatment in STARTS-1 and -2 as a function of originally assigned dose.

Fig. 15.

Hemodynamic improvement after transition from sildenafil to tadalafil for 14 patients on Sildenafil 1; previous catheterization on sildenafil therapy, on Sildenafil 2; last catheterization on sildenafil therapy, on Tadalafil; initial catheterization on tadalafil therapy. For 14 patients, mPAP, PVRI, and the Rp/Rs ratio increased from the previous catheterization (with sildenafil 1) to the last catheterization with sildenafil therapy during the follow-up period of 15.2 ± 8.8 months. After transition to tadalafil, these hemodynamic data significantly improved compared with the last data on sildenafil therapy during the follow-up period of 23.5 ± 8.3 months. mPAP mean pulmonary arterial pressure, PVRI pulmonary vascular resistance index, Rp/Rs ratio pulmonary/systemic vascular resistance ratio with sildenafil. (Adapted from Takatsuki et al.¹¹⁶)

Fig. 16.

Mean pulmonary artery pressure at catheterization before and after initiation of ambrisentan therapy. The figure displays the longitudinal change in mean pulmonary artery pressure before and after initiation of ambrisentan therapy. The time of onset of ambrisentan therapy is zero with the number of months before and after ambrisentan therapy on x -axis. (a) Transition cases ($n = 10$). In 7 of 10 patients with cardiac catheterization data before and after ambrisentan therapy, mean pulmonary artery pressure was improved after transition from bosentan therapy. (b) Add-on cases ($n = 13$). In 11 of 13 patients with cardiac catheterization data before and after ambrisentan therapy, mean pulmonary artery pressure was improved after add-on ambrisentan therapy. (Adapted from Takatsuki et al.¹³⁷).

Table 1
The broad schema of 10 basic categories of pediatric pulmonary hypertensive vascular disease

Category	Description
1	Prenatal or development pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndrome
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders

Source: Cerro et al.⁸.

Table 2
New functional classification for children with pulmonary hypertension

Functional class	Descriptions
Class I	This is defined, at all ages, as children with pulmonary hypertension who are asymptomatic, growing and developing normally, and have no limitation of physical activity. The emphasis on motor development in the first 2 years of life gradually shifts to the child's ability to interact with his/her peers, participate in sporting activities, and go to nursery and then school.
Class II	At all ages, children with pulmonary hypertension are categorized as functional Class II when they have only a slight limitation of physical activity due to fatigue and or dyspnea but are comfortable at rest. Dyspnea can interrupt feeding in young children. At this stage of their disease, most children do not experience syncope or presyncope, but some children can do so while still having a good exercise tolerance. During the first 6 months of life, they fall behind their developmental milestones but continue to grow along their own centiles. Infants and young children are readily fatigued and dyspneic when playing. Beyond 2 years of age, it is important to assess attendance at school or nursery, which should be at least 75% that of healthy children.
Class IIIa	Functional Class IIIa is characterized by marked limitation of physical activity. In addition to failing to achieve their developmental milestones, children between the ages of 6 months and 2 years may show regression of newly learnt activities. Inactivity is noticeable, the child being quiet and taking frequent naps. Less than ordinary activity such as dressing is tiring and can cause dyspnea. Children frequently experience syncope and/or presyncope. Older children can become withdrawn and less confident, choosing to spend time with their families rather than their friends. Growth is compromised and appetite is poor. Nursery/school attendance is less than 50% of normal. The parents frequently say that the child has required excessive medical attention.
Class IIIb	In addition to the features characteristic of Class IIIa, children in Class IIIb often require supplemental feeding by nasogastric tube or gastrostomy. Older children can no longer go to school and although mobile at home they need a wheelchair when venturing out of doors.
Class IV	Children in Class IV are severely compromised and unable to carry out any physical activity without fatigue and/or dyspnea. They are frequently syncopal, may complain of chest pain, and often become quiet and withdrawn. Signs of right heart failure are frequently present, particularly in teenagers.

Source: Lammers et al.²⁹

Table 3
Sildenafil thrice daily dose in the STARTS-1 trial

Body weight (kg)	Sildenafil dose (mg)		
	Low	Medium	High
8–20	NA ^a	10 ^a	20
> 20–45	10	20	40
> 45	10	40	80

Source: Barst et al.¹¹²

^aModeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8- to 20- kg patients (i.e., patients would receive the same dose because of the available tablet strengths); consequently, there was no low dose for this group.