Management of Pulmonary Hypertension in the Pediatric Patient

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KEYWORDS

• Pulmonary hypertension • Pediatric • Diagnosis and management principles

KEY POINTS

- Pediatric pulmonary hypertension (PH), although similar to adult PH, is a unique entity with its own particular pathogeneses, presentation, and management.
- Targeted PH therapies have significantly improved survival in the pediatric PH population in the past 20 years.
- New PH treatments and interventional procedures have shown potential to continue to improve outcomes of children with PH.

INTRODUCTION

Pediatric pulmonary hypertension (PH) is a rare disease with high morbidity and mortality if not diagnosed and treated early. The rarity of sustained pediatric PH has been demonstrated in multiple studies, with an estimated prevalence of 20 to 40 cases per million in Europe. Pulmonary arterial hypertension (PAH), a subset of PH in which the disease is primarily in the precapillary pulmonary arterioles, has a prevalence of 3.0 to 3.7 cases per million children.[1–4]

In the past 20 years, there has been a growing recognition that pediatric PH, although having some similarities to adult PH, is a unique entity with its own particular pathogeneses, presentation, and management.[5,6] Importantly, pediatric PH especially in preterm infants is often a direct sequela of inappropriate lung growth and development and is directly impacted by pulmonary adaptations to fetal and postnatal life. Additional differences between pediatric and adult PH includes their genetic basis, natural history, and responsiveness to PAH-directed therapies.

As experience with adult PAH has grown, targeted PAH therapies have been developed that are increasingly used in younger patients, with sildenafil now approved in children in Europe and bosentan approved for children older than 3 years in the United States. Most of the other medications used in adults including parenteral prostanoids are used in combination therapies for children with significant PAH. Furthermore, interventional strategies like atrial septostomy and reversed Potts shunt in specific patients with severe disease have improved morbidity and mortality.[7,8] Owing to these recent advances, survival of children with PH has significantly improved, with 1-, 5-, and 10-year survivals at 97%, 97%, and 78%.[9] Therapeutic advances have not only increased survival rates but also significantly improved quality of life in children with PAH.[10]

This article reviews the various forms of PH in childhood, with a focus on both established and investigational therapies that are currently available.

DEFINITION AND CLASSIFICATIONS OF PEDIATRIC PULMONARY HYPERTENSION

Pediatric PH is defined as a mean pulmonary artery pressure (mPAP) greater than 20 mm Hg in

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children who are at least 3 months of age.[5] PAH, a subset of PH driven by abnormalities in the precapillary arterioles, is defined as an elevated mPAP greater than 20 mm Hg and pulmonary vascular resistance index (PVRi) (>3 Wood units (WU) × m^2) with normal left heart pressures.[11] These definitions, which were published by the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018,[12] use the cutoff for a normal mPAP of 20 instead of the previously used 25 mm Hg, because mildly increased mPAP (20–24 mm Hg) has been found to independently predict poor survival in adult patients with PH.[13]

The 6th WSPH also refined its universal PH classification system (**Box 2**). This system groups PH into 5 distinct categories, with PAH being group I. As the understanding of the pathobiology of PH has increased, the 6th WSPH made some important changes by expanding the congenital heart disease (CHD) categories, moving hematologic conditions to group V, and also incorporating complex CHD into WSPH Group V PH, which includes PH with unclear and/or multifactorial mechanisms.[12]

The Pulmonary Vascular Research Institute (PVRI) Pediatric Task Force recognizing the multifactorial cause of childhood PH updated the definition and classification system for pediatric PH.[14] The PVRI Task Force also noted that patients with single ventricle physiology and passive pulmonary blood flow can have pulmonary vascular disease even without an elevated mPAP and benefit from further lowering the pulmonary arterial pressures (PAP). Children with cavopulmonary anastomoses are therefore considered to have pulmonary hypertensive vascular disease if the PVRi is greater than 3 WU × m^2 or the transpulmonary gradient is greater than 6 mm Hg, even with normal PAPs by conventional definition.[14]

EPIDEMIOLOGY AND CAUSE

Epidemiologic data regarding pediatric PH are largely derived from PH registries. Although there are multiple adult PAH registries, including the REVEAL [Registry to Evaluate Early and Long-term PAH Disease Management][15] and COMPERA [Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension][16] registries, such robust data collection systems did not initially exist for children. Nonetheless, in the past several years new pediatric PH databases have been developed including the TOPP [Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension] registry, which includes 31 centers from 19 countries[17]; the PPHNet [National Pediatric Pulmonary Hypertension Network], composed of 14 pediatric PH centers in North America and Canada; the Pediatric & Congenital Heart Disease Taskforce of the Pulmonary Vascular Research Institute; and the Spanish Registry of Pediatric Pulmonary Hypertension (REHIPED).

A critical difference between pediatric and adult PH noted in a large comprehensive Netherlands study was the high incidence of "transient" PH in children (87%), which is due to either a repairable cardiac shunt or persistent PH of the newborn.[2] Although the incidence of all types of pediatric PH, including "transient" PH is 63.7 cases/million children/year, the prevalence of sustained PH is about 20 to 40 cases per million in Europe, and the prevalence of PAH is 3.0 to 3.7 cases/million children.[1–4]

In the TOPP registry, the vast majority (88%) of children with PH had PAH (group I), whereas the remaining patients (12%) had PH from respiratory disease such as bronchopulmonary dysplasia (group III). Of the children with PAH, 57% had PAH that was idiopathic (IPAH) or familial (FPAH) and 43% had associated PAH (APAH) in the presence of other disorders like CHD or rheumatologic conditions.

The median age of pediatric PH diagnosis is 7 years, and registries have reported a gender distribution of about 1:1 females:males,[3,4] suggesting a more equal gender distribution in pediatric PH than in adult PH wherein the ratio is closer to 4:1.[18]

Although the cause of pediatric PH is often multifactorial, the genes encoding the transforming growth factor beta/bone morphogenetic protein (TGF-β/BMP) signaling pathway have been linked to the development of PH. This pathway plays an important role in embryonic heart development and systemic vasculogenesis, and mutations in this pathway have been identified in about 80% of children with FPAH and 20% of children with IPAH.[19–21] The genetics of pediatric PH also differs from that of adult PH in the higher incidence of TBX4 mutations and other novel genes in up to 19% of childhood PH.[22,23]

PATHOGENESIS AND PATHOBIOLOGY OF PEDIATRIC PULMONARY HYPERTENSION

The pathogenesis of pediatric PH is complex and heterogeneous. Nevertheless, there are several mechanisms that are fundamental to the development of PH, such as pulmonary vasoconstriction, endothelial dysfunction, cell proliferation with growth dysregulation, inflammation, and in situ thrombosis. These mechanisms must be intimately understood, because they form the basis for targeted therapy in this population.

Vasoconstriction

Pulmonary vasoconstriction and an imbalance in tissue vasoactive mediators has long been recognized as a critical component of PH. In neonates with pediatric PH, the pulmonary vasculature fails to relax as it normally does in transitioning from fetal to neonatal life, and this elevated pulmonary vascular resistance can become fixed as the vasculature itself thickens. In addition, there is a reduction in arteriolar number and vascular surface area. In contrast, older children with IPAH tend to have smooth muscle cell (SMC) hypertrophy that causes vasoconstriction and usually have less of the plexiform lesions and intimal fibrosis that are typically seen in adult PH. Of note, molecular pathways that are crucial in development of all forms of vasoconstriction are the nitric oxide (NO) pathway, prostacyclin pathway, and endothelin pathway.

- *NO pathway*: NO is produced in the endothelium by endothelial NO synthetase (eNOS) and stimulates production of cyclic GMP (cGMP), which is a potent vasodilator and has antiproliferative properties.[24,25] The bioavailability of endothelial NO is decreased in many forms of PAH, and there is often increased production of the phosphodiesterase 5 (PDE 5) enzyme, which degrades cGMP. Asymmetric dimethyl arginine, which is elevated in many forms of PAH, acts by the inhibition of eNOS and via direct effects on gene expression.
- Prostacyclin (PGI2) pathway: PGI2 induces smooth muscle relaxation and prevents platelet aggregation via cyclic AMP production. In patients with PAH, there is a disruption between the balance of PGI2 and vasoactive hormones, which leads to vasoconstriction.
- Endothelin pathway: Endothelin-1 (ET-1) leads to vasoconstriction, fibrogenesis, and cell proliferation and acts via ETA and ETB receptors in the SMC. ET-1 levels are increased in lung tissue and circulation in IPAH, in APAH secondary to lung disease and thromboembolism, as well as in patients with congenital diaphragmatic hernia. ET-1 has been shown to act on SMCs to cause vasoconstriction, cell proliferation, and fibrogenesis.[26]

Endothelial Dysfunction

The endothelium of the pulmonary vasculature helps to produce growth factors and cell signals and is critical in maintaining homeostasis and vascular tone.[27] The triggers of endothelial dysfunction in the patient with PH are not fully understood, but there is often abnormal endothelial activation that causes release of vasoproliferative agents (which promote vascular hyperplasia), as well as vasoconstrictive substances (which lead to worsening vascular obstruction).

Cell Proliferation and Apoptosis

In PH, the smooth muscle and endothelial cells of the pulmonary vasculature are more susceptible to apoptosis, migration, and inappropriate proliferation. There are various growth factors that are abnormally elevated in patients with PAH and play a role in this improper balance, such as vascular endothelial growth factor, tumor necrosis factor-α, and platelet-derived growth factor. Mutations in BMPR2, ALK-1, and endoglin lead to vascular remodeling and are potential pathways for therapeutic intervention.

Inflammation

Inflammation is a known trigger in PAH as evidenced by an increase in cytokines, interleukins, and chemokines[28]; this is most often seen in rheumatological diseases where a rheumatic flare can trigger a PH crisis as well and only subsides with appropriate therapy for the underlying condition. Likewise in childhood PH, especially in preterm infants, lung or systemic infection and inflammation trigger worsening PH and improve with resolution of the inflammatory trigger.

PRESENTATION

Children with PH typically present with exertional dyspnea, fatigue, and failure to thrive. Symptoms are often nonspecific and may be attributed to more common childhood disorders before PH is diagnosed. Syncope especially immediately after exercising or early in the morning just after waking is more common in childhood- (25%) versus adult-onset PH (12%)[17] and may be due to children's increased sensitivity to vasoconstrictive triggers and may actually indicate a vasoresponsive phenotype in selected patients. Patients with unrepaired CHD are less likely to present with syncope but do become more cyanotic with activity or even at rest, because they use cardiac shunts as a "pop-off" for right-to-left blood flow during PH crises. In advanced PH, children may develop right ventricular (RV) failure and subsequent fluid congestion and retention with symptoms of hepatomegaly, peripheral edema, ascites, and even malabsorption due to intestinal wall edema.

PATIENT EVALUATION AND DIAGNOSIS

The diagnostic workup for pediatric PH is similar to that of adults (Fig. 1) and begins with a thorough

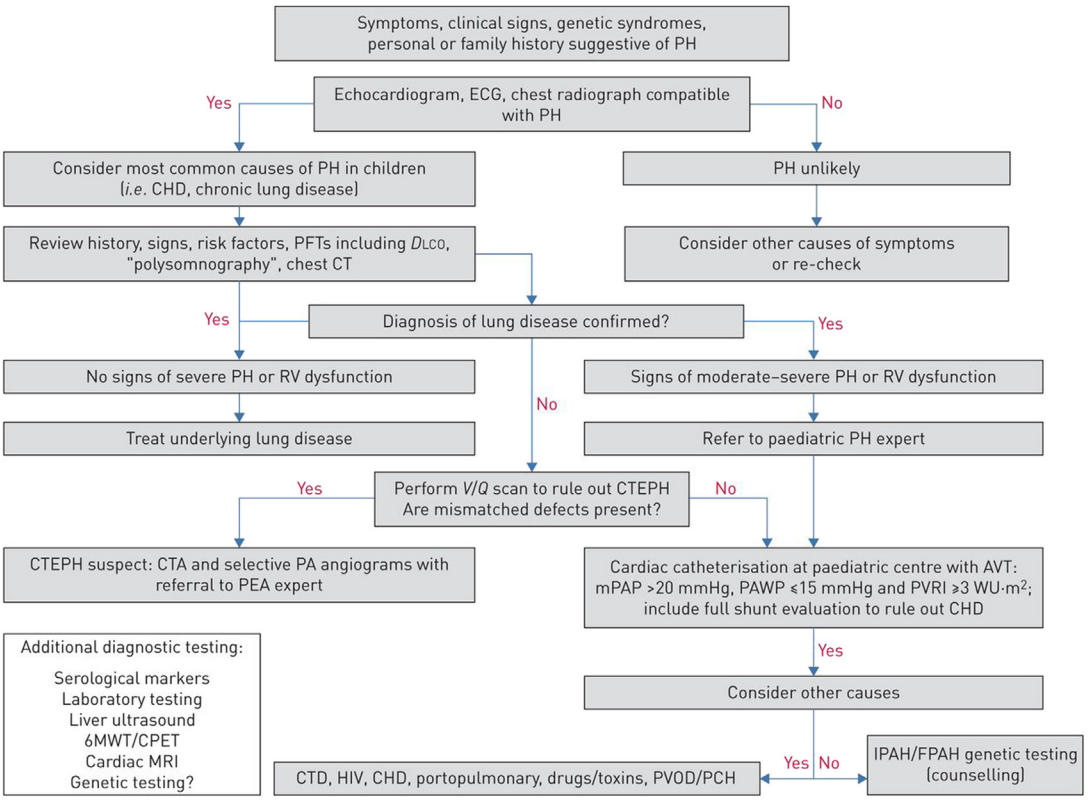

Fig. 1. Diagnostic workup for pediatric pulmonary hypertension. PFT, pulmonary function test; D_{LCO}, diffusing capacity of the lung for carbon monoxide; CT, computed tomography; *V/Q*, ventilation/perfusion; CTEPH, chronic thromboembolic PH; CTA, CT angiography; PA, pulmonary artery; PEA, pulmonary endarterectomy; AVT, acute vasodilator testing; PAWP, pulmonary arterial wedge pressure; PVRi, pulmonary vascular resistance index; WU, Wood units; 6MWT, 6-minute walk test; CPET, cardiopulmonary exercise test; CTD, connective tissue disease; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis. *Reproduced with* permission of the © ERS 2021: European Respiratory Journal 53 (1) 1801916; DOI: 10.1183/13993003.01916- 2018, published January 24, 2019.

individual and family history, physical examination, laboratory tests, genetic evaluation, echocardiography, and ultimately invasive hemodynamic studies. In the initial evaluation of a child with PH, it is also critical to assess for other treatable disorders that may cause PAH and to check for any systemic end-organ injury from PAH such as renal and liver dysfunction.

History and Physical Examination

In addition to obtaining a comprehensive review of systems and complete family history, physicians must pay close attention to a child's growth curve, because failure to thrive and growth retardation can be important signs of chronic disease and right heart failure. A pediatric functional classification system proposed by the PVRI Pediatric Task Force in 2011 takes into account age-related activity and exercise capacity and can be used as part of the clinical evaluation.[29] Vital signs on examination will often show tachypnea and tachycardia, and patients may have decreased oxygen saturation if an intracardiac "pop-off" shunt is present.

On cardiac examination, palpation may reveal a RV heave (from elevated RV pressure), a RV S3 gallop, and a widened second heart sound with a loud pulmonary component and an early systolic click from the dilated pulmonary artery (PA) may be auscultated. Multiple different murmurs may be heard, including a systolic ejection murmur over the dilated PAs, an early diastolic murmur from pulmonary insufficiency at the right upper sternal border, or a systolic murmur at the right lower sternal border if tricuspid regurgitation (TR) is present. If there is severe PH, intracardiac shunts will not generate a murmur because there

is no significant pressure gradient between the right and left ventricles. If there is RV failure, hepatomegaly, ascites, and edema can be present.

Echocardiography

Echocardiography plays a critical role in the diagnosis and monitoring of PH and can be used to check for associated structural heart disease, evaluate cardiac function, risk stratification, and to monitor PAP.

As the RV pressure increases, echocardiography will show ventricular septal flattening and posterior systolic bowing into the left ventricle with systemic or suprasystemic RV pressures (**Fig. 2**). The RV systolic function is difficult to assess because of its complex geometry, but various measures are used to assess for RV dysfunction including tricuspid annular plane systolic excursion, Tei index (which includes both systolic and diastolic time intervals to assess the global cardiac dysfunction), RV fractional area change, and RV ejection fraction.[30] The left ventricular systolic function is typically preserved, although it too can show signs of diastolic dysfunction especially when there is posterior systolic bowing of the ventricular septum. Diastolic dysfunction of the ventricles can be quantified by mitral and tricuspid diastolic inflow velocities, pulmonary and systemic venous flow patterns, RV myocardial performance index, and tissue Doppler imaging of the mitral and tricuspid annulus and at the septum.

RV systolic pressure can be determined by measuring the peak systolic pressure gradient from the RV to the right atrium and is calculated by using the Bernoulli equation $P = 4\ v^2$, where v is the maximum velocity of the TR jet measured by continuous wave Doppler. Assuming there is no obstruction between the RV to the PA, the TR jet can also be used to estimate the PA pressure and severity of PH (see **Fig. 2**). Clinicians, however, will often rely on additional echocardiographic findings that are suggestive of PH, such as ventricular septal position and motion, systemic to pulmonary shunt gradients at the ventricular or great artery levels, and pulmonary regurgitation Doppler gradients, because there may not be an adequate TR Doppler envelope to estimate pressures and TR jet velocity can overestimate or underestimate the PA pressure especially with nonsedated echocardiograms.[31,32] Of note, echocardiography protocols are available for the pediatric patient with PH (**Box 1**)[33] and should be used for both diagnosis and long-term monitoring of children with PH.

Cardiac Catheterization

Right heart catheterization is considered the gold standard for diagnosing PH and allows for direct measurement of PA pressure and PVR. In 2019, the 6th WSPH modified their criteria for adult PH to include a mean PA pressure greater than 20 mm Hg and a PVR 3 WU[12] or more, and the pediatric task force adopted these criteria as well.[5] Inclusion of PVR in the definition of pediatric PH is particularly useful because, as discussed previously, many children with single ventricle physiology can have normal PA pressures but even mildly elevated pulmonary vascular resistances can lead to severe physiologic consequences and Fontan failure.

During cardiac catheterization, acute vasodilator testing (AVT) (usually with inhaled NO [iNO]) should also be performed. Other medications including inhaled prostanoids have also been used for AVT but are not standardized. AVT responsiveness in adults is defined as a decrease

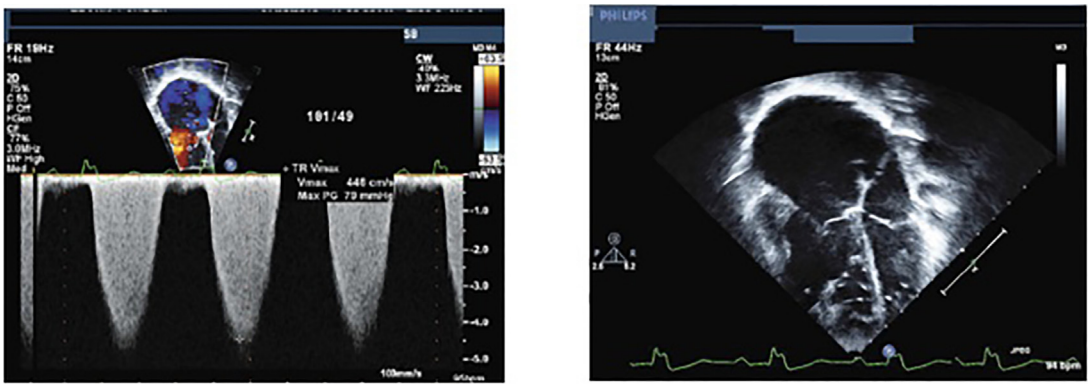

Fig. 2. Echocardiography findings in patients with pulmonary hypertension. (*Left*) Echocardiography continuous wave Doppler imaging across the tricuspid valve showing measurements of the tricuspid valve regurgitation jet using the Bernoulli principle. (*Right*) Apical 4-chamber imaging showing a dilated right atrium and right ventricle, with bowing of the atrial and ventricular septum to the left.

Box 1
Transthoracic echocardiography protocol in pediatric patients with pulmonary hypertension

Variables to be assessed
Estimation of the systolic PAP through the TR jet velocity by CW Doppler
Estimation of mean PAP and end diastolic PAP through CW Doppler of the PR jet
PAAT
RV longitudinal systolic function (eg, TAPSE)
RV fractional area change
RV strain and strain rate measurements
RV systolic to diastolic duration ratio by CW Doppler of the TR jet
Tissue Doppler velocities (eg, E′, A′ and S′)
RV myocardial performance (Tei) index
RV/LV diameter ratio
LV EI (Eccentricity Index)

RV and RA enlargement.

CW, continuous wave; LV, left ventricle; PR, pulmonary regurgita; RA, right atrium; S′, peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiography; PAAT, pulmonary artery acceleration time; LV EI, left ventricular eccentricity index.

Note: TTE alone is not sufficient to initiate a targeted therapy.

Koestenberger M, Friedberg MK, Nestaas E, et al. Transthoracic echocardiography in the evaluation of pediatric pulmonary hypertension and ventricular dysfunction. Pulm Circ. 2016;6(1):15–29. https://doi.org/10.1086/68505. © Sage Publications Ltd. 2021. Reprinted by permission of SAGE publications.

in mPAP by at least 10 mm Hg to a value of less than 40 mm Hg with sustained cardiac output, or in subjects with baseline mPAP less than 40 mm Hg as a drop of at least 10 mm Hg without a decrease in cardiac output.[5] This definition has been shown to successfully identify patients who will have sustained benefit from calcium channel blocker (CCB) therapy with much better long-term outcomes and should therefore be used in pediatric population as well.[34] In fact, the 6th WSPH have included these patients as a separate category WSPH, group 1.5 (see **Box 2**).

The 6-Minute Walk Test and Cardiopulmonary Exercise Testing

The 6-minute walk test is useful to assess functional capacity, monitor response to therapy, and predict outcomes. Using an actigraph, or a noninvasive monitor of patients' activity levels, provides a continuous real-time monitoring tool and is an attractive option for evaluating activity in patients with PH.[35] Cardiopulmonary exercise testing is another testing modality that has been shown to provide cardiorespiratory parameters that correlate with the degree of pulmonary vascular resistance and disease severity in children[36,37] and can reliably be performed in patients who are at least 7 years old. These tests are performed at 3- to 6-month intervals to guide response to therapy and indicate further interventions or escalation.

Box 2
Updated clinical classification of pulmonary hypertension

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

LVEF, left ventricular ejection fraction; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease.

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Risk Assessment

Risk assessment scores have been available for adult PH; however, it is only recently that the

European Society of Cardiology/European Respiratory Society guidelines and the 6th WSPH proceedings recommended risk scoring for pediatric PAH using the REVEAL registry and the European registries. Pediatric patients with PH had lower median risk scores when compared with adults, but 1-year survival for each risk group was similar to adults, although they separated at 5 years.[38]

TREATMENT

Although there is no uniform therapeutic approach for all children with PH, various treatments have been developed that can improve the survival of pediatric patients with PH.[39,40] As most children with PH have some degree of precapillary PAH, targeted therapies discussed later are geared toward the pediatric patient with PAH. A synopsis of the guidelines specifically for pediatric IPAH/FPAH management is outlined in **Fig. 3** and is reviewed in further depth in the following sections (along with general PAH treatment).

GENERAL MEASURES AND THE PRIMARY CARE PHYSICIAN

Managing children with PH is a team effort with the pediatrician playing an important role. Any fevers should be treated early with antipyretics, to decrease the metabolic demands on an already tenuous cardiorespiratory system. Respiratory infections, which are quite common in children, can trigger hypoxemia and a PH crisis if not treated aggressively. Some children may require iNO during an acute respiratory illness if they are hospitalized with severe PH. Decongestants containing pseudoephedrine are contraindicated because they can worsen PH symptoms, but antitussives are sometimes used especially if there is a risk of coughing-induced hemoptysis. Annual influenza and pneumococcal vaccines should be provided for primary prevention of respiratory illnesses. Coronavirus disease 2019 vaccination is recommended in children with PH older than 16 years, and currently clinical trials are underway in younger children.

It is also important that pediatricians provide dietary recommendations and even medical therapy to prevent constipation, because straining with bowel movements can decrease venous return to the right side of the heart and can cause a syncopal event. A thorough psychosocial evaluation and close follow-up is highly recommended to identify and manage issues that may impact the quality of life of these fragile patients.

Several goals of targeted therapy for PAH are as follows:

1. Improvement of symptoms and quality of life
2. Improvement of hemodynamics
3. Halting progression of disease
4. Reversal of established pulmonary vascular disease and cardiac hypertrophy (if possible)
5. Reduction of morbidity
6. Increasing life expectancy with the disease

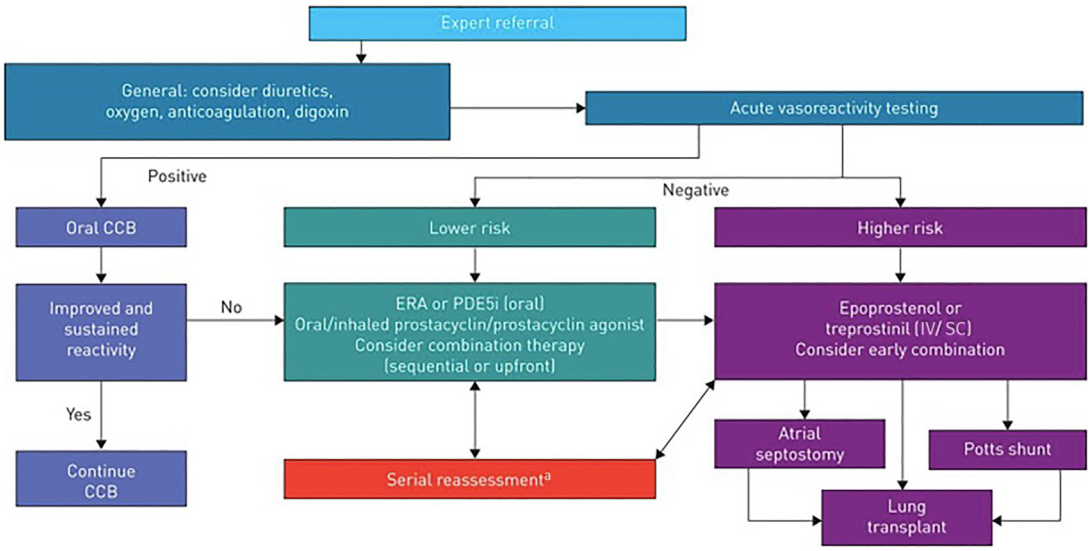

Fig. 3. Pediatric idiopathic and familial pulmonary arterial hypertension treatment algorithm. ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase type 5 inhibitor; IV, intravenous; SC, subcutaneous. [a]Deterioration or not meeting treatment goals. Reproduced with permission of the © ERS 2021: European Respiratory Journal 53 (1) 1801916; DOI: 10.1183/13993003.01916- 2018, published January 24, 2019.

Medical Therapy

Calcium channel blockade

CCBs, which prevent calcium influx into smooth and cardiac muscles, have been shown to be potent pulmonary vasodilators for patients who are "responders" to AVT. Only 5% to 10% of adults with PAH are considered AVT "responders,"[41] whereas some studies have suggested that the response rate in children may be as high as 40%,[9] although other research has not shown such a difference in vasoreactivity.[42] Of note, children with CHD are significantly less likely be AVT responsive, and therefore CCBs often do not help improve PAH in this subgroup.[42] CCBs are only used in children older than 1 year and are contraindicated in AVT nonresponders.

The optimal dosing of CCBs in children has not been established. Studies typically report using relatively high doses of CCBs, such as amlodipine 20 to 40 mg daily and long-acting nifedipine 120 to 240 mg daily, but the optimal dosing of drugs in pediatric PAH is still unknown.

Nitric oxide

inhaled Nitric Oxide (iNO) causes smooth muscle relaxation of the pulmonary vasculature by activating guanylate cyclase and increasing cGMP.[24] iNO may also prevent platelet adhesion to arterial walls via its antiproliferative effect on smooth muscle. iNO in doses of 1 to 20 ppm is used in a multitude of scenarios including treatment of an acute PAH crisis, following cardiac surgery, during right heart catheterization for AVT, and for treatment of persistent PH in the newborn.[43] Weaning iNO has to be done carefully in a carefully monitored intensive care unit setting and often may need to be weaned in fractions of 1 ppm to prevent rebound PH. Sildenafil has been used especially in the postoperative setting as a cGMP donor while weaning off iNO.[44]

Phosphodiesterase inhibitors

Like NO, phosphodiesterase 5 (PDE5) inhibitors cause pulmonary vasodilation by increasing cGMP levels in smooth muscle. PDE5 inhibitors were initially used in patients being weaned off iNO postoperatively,[44] but now they are often first-line therapy along with other medications in treatment of PAH. PDE5 inhibitors have been shown to improve symptoms in pediatric patients with PH, both when used alone and when they are administered as part of combination therapy with prostacyclins.[45,46]

The STARTS-1 trial, a double-blind, multicenter, placebo-controlled study, showed that the PDE5 inhibitor sildenafil improved the functional class and maximal aerobic capacity of pediatric patients with PAH patients.[47] Although its extension study, the STARTS-2 trial, found that children randomized to higher doses of sildenafil had increased mortality, all sildenafil groups (including the high-dose sildenafil group) had increased survival compared with placebo.[48] Because increased sildenafil dosing was associated with increased mortality, the US Food and Drug Administration (FDA) in 2012 initially advised that chronic sildenafil use was "not recommended in children," but later revised their recommendations to state that there "may be situations in which the risk-benefit profile" of sildenafil "may be acceptable in individual children but should only be administered under expert guidance."[49] Based on the STARTS trial data, sildenafil was approved for use in Europe by the European Medicines Agency.

Sildenafil is typically administered 3 times a day and is enterally dosed as 1 mg/kg per dose in infants, 10 mg for children weighing 10 to 20 kg, and 20 mg per dose for children weighing greater than 20 kg. The intravenous dose is half of the enteral dose. Sildenafil is usually slowly uptitrated to reach the final dose to prevent hypotension and monitor for other side effects. Tadalafil, a newer PDE5 inhibitor, is an attractive alternative to sildenafil, because it is dosed once a day with a similar side effect profile.[50]

Endothelin receptor antagonists

Endothelin-1 (ET-1) is a potent pulmonary vasoconstrictor that is elevated in many patients with PAH, and its level inversely correlates with prognosis. Bosentan, an oral endothelin receptor antagonist (ERA), is now FDA approved in children older than 3 years in the United States. An open-label study in children with group I PAH showed bosentan to be well tolerated and improve hemodynamics at 12-week follow-up.[51,52] Side effects of bosentan include hepatotoxicity and teratogenicity. Bosentan is given at 1 mg/kg per dose twice a day and increased to 2 mg/kg per dose after 2 to 4 weeks, while monitoring liver enzymes. Patients on stable bosentan doses require monthly liver function testing, and postmenarchal girls require monthly pregnancy testing and dual contraception, to prevent teratogenicity of the medication. Ambrisentan is a selective ERA that has been associated with less hepatoxicity and can be administered once daily.[53] Macitentan, a tissue-specific ERA, is now undergoing trials in the pediatric age group.[54] All ERAs are known to be teratogenic in animal studies and hence have the same pregnancy testing and dual contraception instructions.

Prostacyclins

The discovery of prostacyclin's pulmonary vasodilatory effects in the early 1990s revolutionized the

medical management of PAH, because its use significantly improved survival and quality of life. Importantly, prostacyclins show a survival benefit even in patients who are unresponsive to AVT, implying that prostacyclin is not only a pulmonary vasodilator but possibly promotes pulmonary vascular remodeling as well.

Epoprostenol, an intravenous prostacyclin, can be chronically administered and has been shown to prolong survival, improve cardiac output, increase exercise capacity, positively alter hemodynamics, and prolong survival in children with PAH.[55,56] Epoprostenol dosing (ng/kg/min) is slowly uptitrated starting at 1 to 2 ng/kg/min to over 100 ng/kg/min.

Because epoprostenol has a very short half-life of 1 to 2 minutes and is chemically unstable at room temperature, it must be delivered using a continuous infusion system with cold packs and a central venous line is typically needed. This form of drug administration is associated with its own challenges including clots and line occlusion, catheter and systemic infection, and pump malfunction, which can either lead to an inadvertent bolus (causing systemic hypotension) or interruption (causing rebound PAH) of epoprostenol. These difficulties have led to a search for alternative forms of prostacyclin that would allow for oral, inhaled, subcutaneous, or long-acting intravenous delivery.

Prostacyclin analogues

Treprostinil sodium can be administered both subcutaneously and intravenously, and in its subcutaneous form the complications of having a central venous line can be avoided. Recent research has described the successful use of subcutaneous treprostinil in young children.[57] Discomfort at the infusion site has been reported, although no other serious side effects related to subcutaneous treprostinil have been noted.[58] Infusion site pain has been noted to be lower in infants when compared with older patients.[57]

Oral prostacyclin analogues Oral treprostinil was approved by the US FDA in 2013 for use in adults with PAH. Although treprostinil has been shown to improve exercise capacity in PAH,[59] it has a significant side effect profile including headaches and gastrointestinal symptoms, and a recent pediatric study found that half of children who were initiated on the drug had stopped it within 2 years mostly because of its side effects.[60]

Other oral prostacyclin analogues include beraprost sodium, which has been approved for PAH in Japan but not in the Europe and the United States, and oral selexipag, a prostacyclin receptor agonist that has also been shown to decrease the risk of PAH complications and death.[61,62]

Inhaled prostacyclin analogues Inhaled prostacyclins are an attractive choice for prostacyclin administration, because their selective delivery to the lungs avoids more systemic side effects. Direct airway delivery is also thought to cause less V-Q mismatch. Inhaled iloprost has a short half-life of 20 to 25 minutes and must be given every 1 to 4 hours,[43] whereas inhaled treprostinil with its longer half-life can be administered every 6 hours and has been shown to improve exercise capacity and is safe and well tolerated in the pediatric population.[63]

Combination therapy

Similar to cancer therapy experience, combination therapy to target multiple pathways simultaneously has shown benefit in PH therapy. The AMBITION trial demonstrated that the risk of clinical failure was 50% lower in adults on a combination of ambrisentan and tadalafil when compared with monotherapy using either drug.[45] A recent pediatric study including patients with PAH from two US and one European center demonstrated that treatment with combination therapy was strongly associated with improved survival when compared with monotherapy.[39]

Anticoagulation

The role of chronic anticoagulation in pediatric patients with PAH is based on recent adult IPAH studies, which have demonstrated that many adults with IPAH have small PA thromboses on lung pathology. Although the adult COMPERA registry suggested that anticoagulation in adult patients with IPAH is associated with improved survival,[64] the REVEAL registry concluded that anticoagulation is not advantageous and can in certain scenarios even worsen survival.[65] As there is no research to support use of anticoagulation in pediatric PAH, it is currently only used in children with coagulation disorders, significant ventricular systolic dysfunction, thromboembolic PH, and those patients with indwelling lines or minipumps to prevent line occlusion via clot formation.

Novel therapies, ongoing clinical trials, and investigational drugs

Antiproliferative drugs Early PAH management had focused on medications that would cause pulmonary vasodilation. In the last 10 years, however, we have learned that additional pathobiologic mechanisms are involved in PH, including unbridled cell proliferation in the smooth muscle and adventitia of PAs. Some newer PH medications, which were borrowed from the oncology world,

target this mechanism. Imatinib, a tyrosine kinase inhibitor that is used to treat chronic myeloid leukemia, inhibits a growth factor receptor on SMCs and has shown early signs of improving symptoms in adults with advanced PAH.[66] Everolimus is another antineoplastic drug, which is an mTOR inhibitor, and in pilot studies has improved PVR and exercise tolerance in children with PAH.[67] Sirolimus has been studied in children with pulmonary vein stenosis in an attempt to halt the progression of disease.[68]

Rho-Kinase inhibitors The RhoA-/Rho-kinase signaling pathway effects vasorelaxation, and when activated can cause sustained SMC contraction. Studies show that drugs that block the rho-kinase pathway, like fasudil, can decrease PAPs in animals with PAH that is refractory to prostanoids and iNO, although this has not been reproduced in humans.[69,70]

Gene therapy With new understanding of the genetic basis of PAH, research has also turned to gene replacement as possible therapy for PAH. Advances in genetic therapy may ultimately hold the key to early detection and perhaps even cure for specific children with known genetic mutations, such as the 2q33 (TGF-β receptor) mutation associated with HPAH and IPAH.[71]

Interventional Therapy

Atrial septostomy

In children with severe PH, an atrial communication allows cardiac output to be maintained via right to left shunting even during a PH crisis. Thus, patients who have PAH with right heart failure or recurrent syncope, but do not have a patent foramen ovale, can benefit clinically and hemodynamically from an atrial septostomy.[8,72] This procedure has been shown to increase survival (1- and 2-year survival is 87% and 76%, respectively, compared with 64% and 42% using conventional therapy alone).

This invasive procedure is associated with significant risks and is usually only performed in patients with syncope or right heart failure despite maximal medical therapy, and potentially as a bridge to transplantation.

Potts shunt

A reverse Potts shunt, which allows for right to left flow from the left PA to the descending aorta, can also help to decompress the RV in the setting of significant PH and can improve hemodynamics and outcomes in the severely ill child.[7,73–77] Unidirectional valved Potts shunts can be used to minimize left to right flow across the shunt when pulmonary pressures drop.[76] A transcatheter approach for placement of the Potts shunt has been suggested as a possible option as well.[77] Use of Potts shunt may improve quality of life as well as survival to transplant.

Lung transplantation

A small number of centers perform pediatric lung transplantation for patients with PAH. Survival rates for patients with PAH who have undergone lung transplantation are quite low: the 1-year, 5-year, and 10-year survivals are 64%, 44%, and 20%, respectively.[78,79] Transplantation should therefore be considered for children who are World Health Organization functional class IV despite maximal medical therapy, and ideally children should be listed when their probability of 2-year survival is less than 50%. Extracorporeal membrane oxygenation, either as a bridge to recovery or to transplant, can also be a feasible option in certain patients.

SUMMARY

Owing to recent advances in PH therapy, children with PH have significantly improved survival, hemodynamics, and quality of life. Patients who are responsive to AVT benefit from CCBs, whereas nonresponsive patients can be assisted with prostanoids and ERAs. Multiple new treatments are on the horizon and have shown promise in adult PAH populations. As our understanding of the genetic basis and pathobiologic mechanisms of PH continue to evolve, we hope that in the future we will be able to better treat, and potentially cure, this disease.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. 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(2):66–74.
2. Van Loon L, Roofthooft M, Hillege HL, et al. Pediatric Pulmonary Hypertension in the Netherlands Epidemiology and Characterization During the Period 1991 to 2005. 2011. doi:10.1161/CIRCULATIONAHA.
3. Li L, Jick S, Breitenstein S, et al. Pulmonary arterial hypertension in the USA: an epidemiological study in a large insured pediatric population. Pulm Circ 2017;7(1):126–36.
4. Mańin MJDC, Rotés AS, Ogando AR, et al. Assessing pulmonary hypertensive vascular disease in

childhood data from the Spanish registry. Am J Respir Crit Care Med 2014;190(12):1421–9.
5. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53(1). https://doi.org/10.1183/13993003.01916-2018.
6. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1). https://doi.org/10.1183/13993003.01913-2018.
7. Baruteau AE, Serraf A, Lévy M, et al. Potts shunt in children with idiopathic pulmonary arterial hypertension: long-term results. Ann Thorac Surg 2012;94(3):817–24.
8. Micheletti A, Hislop AA, Lammers A, et al. Role of atrial septostomy in the treatment of children with pulmonary arterial hypertension. Heart 2006;92(7):969–72.
9. Yung D, Widlitz AC, Rosenzweig EB, et al. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation 2004;110(6):660–5.
10. Mullen MP, Andrus J, Labella MH, et al. Quality of life and parental Adjustment in pediatric pulmonary hypertension. Chest 2014;145(2). https://doi.org/10.1378/chest.13-0636.
11. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 Updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Hear Lung Transpl 2019;38(9):879–901.
12. Galiè N, McLaughlin VV, Rubin LJ, et al. An overview of the 6th World Symposium on pulmonary hypertension. Eur Respir J 2019;53(1). https://doi.org/10.1183/13993003.02148-2018.
13. Douschan P, Kovacs G, Avian A, et al. Mild elevation of pulmonary arterial pressure as a predictor of mortality. Am J Respir Crit Care Med 2018;197(4):509–16.
14. Del 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(2):286–98.
15. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 2010;122(2):164–72.
16. Hoeper MM, Pausch C, Grünig E, et al. Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. J Hear Lung Transpl 2020;39(12):1435–44.
17. Berger RMF, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379(9815):537–46.
18. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline Characteristics from the REVEAL registry. Chest 2010;137(2). https://doi.org/10.1378/chest.09-1140.
19. Zhu N, Welch CL, Wang J, et al. Rare variants in SOX17 are associated with pulmonary arterial hypertension with congenital heart disease. Genome Med 2018;10(1). https://doi.org/10.1186/s13073-018-0566-x.
20. Levy M, Eyries M, Szezepanski I, et al. Genetic analyses in a cohort of children with pulmonary hypertension. Eur Respir J 2016;48(4):1118–26.
21. Pfarr N, Fischer C, Ehlken N, et al. Hemodynamic and genetic Analysis in children with idiopathic, Heritable, and congenital heart disease associated pulmonary arterial hypertension. Respir Res 2013;14(1):3. https://doi.org/10.1186/1465-9921-14-3.
22. Zhu N, Gonzaga-Jauregui C, Welch CL, et al. Exome Sequencing in children with pulmonary arterial hypertension Demonstrates differences compared with adults. Circ Genomic Precis Med 2018;11(4):e001887.
23. Kerstjens-Frederikse WS, Bongers EMHF, Roofthooft MTR, et al. TBX4 mutations (small patella syndrome) are associated with childhood-onset pulmonary arterial hypertension. J Med Genet 2013;50(8):500–6.
24. Rosenzweig EB, Barst RJ. Congenital heart disease and pulmonary hypertension: Pharmacology and feasibility of late surgery. Prog Cardiovasc Dis 2012;55(2):128–33.
25. Bradley EA, Chakinala M, Billadello JJ. Usefulness of medical therapy for pulmonary hypertension and delayed atrial septal defect closure. Am J Cardiol 2013;112(9):1471–6.
26. Sauvageau S, Thorin E, Caron A, et al. Endothelin-1-Induced pulmonary Vasoreactivity is Regulated by ETA and ETB receptor Interactions. J Vasc Res 2007;44(5). https://doi.org/10.1159/000102534.
27. Veyssier-Belot C, Cacoub P. Role of endothelial and smooth muscle cells in the physiopathology and treatment management of pulmonary hypertension. Cardiovasc Res 1999;44:274–82.
28. Hassoun PM, Mouthon L, Barberà JA, et al. Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol 2009;54(1 Suppl):S10–9. https://doi.org/10.1016/j.jacc.2009.04.006.
29. Lammers AE, Adatia I, Del Cerro MJ, et al. Functional classification of pulmonary hypertension in children: report from the PVRI pediatric taskforce, Panama 2011. Pulm Circ 2011;1(2):280–5.
30. Grünig E, Peacock AJ. Imaging the heart in pulmonary hypertension: an update. Eur Respir Rev 2015;24(138):653–64.
31. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic

assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179(7):615–21.
32. Greiner S, Jud A, Aurich M, et al. Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. J Am Heart Assoc 2014;3(4). https://doi.org/10.1161/JAHA.114.001103.
33. Koestenberger M, Friedberg MK, Nestaas E, et al. Transthoracic echocardiography in the evaluation of pediatric pulmonary hypertension and ventricular dysfunction. Pulm Circ 2016;6(1):15–29.
34. Douwes JM, Humpl T, Bonnet D, et al. Acute vasodilator response in pediatric pulmonary arterial hypertension current clinical Practice from the TOPP registry. J Am Coll Cardiol 2016;67(11):1312–23.
35. Ulrich S, Fischler M, Speich R, et al. Wrist Actigraphy predicts outcome in patients with pulmonary hypertension. Respiration 2013;86(1). https://doi.org/10.1159/000342351.
36. Yetman AT, Taylor AL, Doran A, et al. Utility of cardiopulmonary stress testing in assessing disease severity in children with pulmonary arterial hypertension. Am J Cardiol 2005;95(5):697–9.
37. Wensel R, Francis DP, Meyer FJ, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol 2013;167(4):1193–8.
38. Ivy D, Rosenzweig EB, Elliott C, et al. Risk assessment in pediatric patients with pulmonary arterial hypertension (PAH): Application of the REVEAL 2.0 risk calculator. Chest 2019;156(4):A169–71.
39. Zijlstra WMH, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: Clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol 2014;63(20):2159–69.
40. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension. Circulation 2015;132(21):2037–99.
41. Malhotra R, Hess D, Lewis GD, et al. Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension. Pulm Circ 2011;1(2):250–8.
42. Douwes JM, Van Loon RLE, 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(24):3137–46.
43. Davidson D, Barefield ES, Kattwinkel J, et al. Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the Term Newborn: A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study. Pediatrics. 101(3 Pt 1):32534.
44. Trachte AL, Lobato EB, Urdaneta F, et al. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann Thorac Surg 2005;79(1):194–7.
45. Galiè N, Barberà JA, Frost AE, et al. Initial Use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373(9):834–44.
46. Cohen JL, Nees SN, Valencia GA, et al. Sildenafil Use in children with pulmonary hypertension. J Pediatr 2019;205:29–34.e1.
47. 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(2):324–34.
48. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation 2014;129(19):1914–23.
49. FDA drug safety communication: FDA clarifies Warning about pediatric Use of Revatio (sildenafil) for pulmonary arterial hypertension. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-clarifies-warning-about-pediatric-use-revatio-sildenafil-pulmonary. Accessed August 30, 2012.
50. Takatsuki S, Calderbank M, Ivy DD. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. Pediatr Cardiol 2012;33(5):683–8.
51. 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(4):697–704.
52. Hislop AA, Moledina S, Foster H, et al. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J 2011;38(1):70–7.
53. Takatsuki S, Rosenzweig EB, Zuckerman W, et al. Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. Pediatr Pulmonol 2013;48(1):27–34.
54. Schweintzger S, Koestenberger M, Schlagenhauf A, et al. Safety and efficacy of the endothelin receptor antagonist macitentan in pediatric pulmonary hypertension. Cardiovasc Diagn Ther 2020;10(5). https://doi.org/10.21037/cdt.2020.04.01.
55. Lammers AE, Hislop AA, Flynn Y, et al. Epoprostenol treatment in children with severe pulmonary hypertension. Heart 2007;93(6):739–43.
56. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106(12):1477–82.
57. Ferdman DJ, Rosenzweig EB, Zuckerman WA, et al. Subcutaneous treprostinil for pulmonary hypertension in chronic lung disease of infancy. Pediatrics 2014;134(1). https://doi.org/10.1542/peds.2013-2330.

58. McLaughlin VV, Gaine SP, Barst RJ. Efficacy and safety of treprostinil: an epoprostenol analog for Primary pulmonary hypertension. J Cardiovasc Pharmacol 2003;41(2):293–9.
59. Feldman J, Habib N, Radosevich J, et al. Oral treprostinil in the treatment of pulmonary arterial hypertension. Expert Opin Pharmacother 2017;18(15): 1661–7.
60. Kanaan U, Varghese NP, Coleman RD, et al. Oral treprostinil use in children: a multicenter, observational experience. Pulm Circ 2019;9(3). https://doi.org/10.1177/2045894019862138.
61. Coghlan JG, Channick R, Chin K, et al. Targeting the prostacyclin pathway with selexipag in patients with pulmonary arterial hypertension Receiving double combination therapy: Insights from the randomized controlled GRIPHON study. Am J Cardiovasc Drugs 2018;18(1):37–47.
62. Sitbon O, Morrell NW. Pathways in pulmonary arterial hypertension: the future is here. Eur Respir Rev 2012;21(126):321–7.
63. 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(11):1704–9.
64. Olsson KM, Delcroix M, Ghofrani HA, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the comparative, prospective registry of newly initiated therapies for pulmonary hypertension (COMPERA). Circulation 2014;129(1): 57–65.
65. Preston IR, Roberts KE, Miller DP, et al. Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the registry to evaluate early and Long-Term PAH Disease Management (REVEAL). Circulation 2015;132(25): 2403–11.
66. Ghofrani HA, Morrell NW, Hoeper MM, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. Am J Respir Crit Care Med 2010;182(9):1171–7.
67. Seyfarth HJ, Hammerschmidt S, Halank M, et al. Everolimus in patients with severe pulmonary hypertension: a safety and efficacy pilot trial. Pulm Circ 2013;3(3):632–8.
68. Callahan R, Esch JJ, Wang G, et al. Systemic Sirolimus to prevent in-Stent stenosis in pediatric pulmonary vein stenosis. Pediatr Cardiol 2020;41(2). https://doi.org/10.1007/s00246-019-02253-6.
69. Fukumoto Y, Matoba T, Ito A, et al. Acute vasodilator effects of a Rho-kinase inhibitor, fasudil, in patients with severe pulmonary hypertension. Heart 2005; 91(3):391–2.
70. Mcnamara PJ, Murthy P, Kantores C, et al. Acute vasodilator effects of Rho-kinase inhibitors in neonatal rats with pulmonary hypertension unresponsive to nitric oxide. Am J Physiol Lung Cell Mol Physiol 2008;294:205–13.
71. Said SI, Hamidi SA. Pharmacogenomics in pulmonary arterial hypertension: toward a mechanistic, target-based approach to therapy. Pulm Circ 2011; 1(3):383–8.
72. Chiu JS, Zuckerman WA, Turner ME, et al. Balloon atrial septostomy in pulmonary arterial hypertension: effect on survival and associated outcomes. J Hear Lung Transpl 2015;34(3):376–80.
73. Baruteau AE, Belli E, Boudjemline Y, et al. Palliative Potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: updated data from the first 24 patients. Eur J Cardio-thoracic Surg 2015;47(3):e105–10.
74. Grady RM, Eghtesady P. Potts shunt and pediatric pulmonary hypertension: what We have learned. Ann Thorac Surg 2016;101(4):1539–43.
75. Esch JJ, Shah PB, Cockrill BA, et al. Transcatheter Potts shunt creation in patients with severe pulmonary arterial hypertension: initial clinical experience. J Hear Lung Transpl 2013;32(4):381–7.
76. Rosenzweig EB, Ankola A, Krishnan U, et al. A novel unidirectional-valved shunt approach for end-stage pulmonary arterial hypertension: Early experience in adolescents and adults. J Thorac Cardiovasc Surg 2021;161(4):1438–46.e2. https://doi.org/10.1016/j.jtcvs.2019.10.149.
77. Boudjemline Y, Sizarov A, Malekzadeh-Milani S, et al. Safety and feasibility of the transcatheter approach to Create a reverse Potts shunt in children with idiopathic pulmonary arterial hypertension. Can J Cardiol 2017;33(9):1188–96.
78. Lordan JL, Corris PA. Pulmonary arterial hypertension and lung transplantation. Expert Rev Respir Med 2011;5(3):441–54.
79. Galie N, Manes A, Palazzini M, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs 2008;68(8):1049–66.