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CONGENITAL HEART DISEASE (RA KRASUSKI, SECTION EDITOR)

Management of Pulmonary Arterial Hypertension in the Pediatric Patient

Jordan E. Ezekian[1] · Kevin D. Hill[1]

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Abstract

Purpose of Review Pediatric pulmonary arterial hypertension (PAH) is associated with significant morbidity and mortality. Herein we review the diagnosis and classification for pediatric PAH and detail the current therapeutic options available for use in the pediatric PAH population.

Recent Findings Classification and treatment of pediatric PAH is guided by adult criteria and treatment algorithms, yet the distribution of factors contributing to PAH in children differs significantly from that seen in adults. It is necessary to understand these differences in order to appropriately tailor therapy to the needs of the child or adolescent. An expanding array of targeted PAH drugs are now approved for use in adults, and many of these drugs are used "off-label" to treat children and adolescents with PAH. Use of these novel therapies has coincided with marked improvement in outcomes, suggesting significant benefit. However, because most of these drugs have not been studied in rigorous randomized, controlled trials in children, it is critical that physicians understand their mechanisms of action, potential benefits, and safety profiles.

Summary Pediatric PAH outcomes have improved substantially in the modern era, coinciding with the "off-label" use of targeted PAH drugs in children and adolescents. Ideally, care should be provided at centers with specialized expertise in the diagnosis and treatment of pediatric PAH by providers who understand the appropriate diagnostic algorithms, classification schemes, and treatment approaches.

Keywords Pediatric pulmonary arterial hypertension · Pulmonary hypertension · Phosphodiesterdase-5 inhibitors · Endothelin receptor antagonists · Nitric oxide · Prostacyclins

Introduction

Pediatric pulmonary hypertension (PH) is a rare disease that affects approximately 15–30 out of every one million children [1, 2]. Untreated, a childhood diagnosis of PH portends a poor prognosis with historical mean survival following a diagnosis of idiopathic or primary PH of less than 1 year [3]. Improved understanding of the pathophysiology of PH has led to innovations which have expanded therapeutic options for adults with PH. Although the majority of these targeted therapies have not been well studied in children, "off-label" use has coincided with marked improvements in pediatric PH outcomes; 3-year survival has ranged from 80 to 91% in several, large, multinational contemporary studies [1, 3–6]. A major challenge in advancing treatment of pediatric PH is the need for rigorous clinical trial data to guide dosing, safety, and efficacy of targeted PH therapies. Here we will briefly review the diagnosis and classification of PH with a primary focus on the current available therapeutic options.

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✉ Kevin D. Hill
kevin.hill@duke.edu

Jordan E. Ezekian
Jordan.ezekian@duke.edu

[1] Department of Pediatrics, Division of Pediatric Cardiology, Duke University Medical Center, 2301 Erwin Road, DUMC, Box 3090, Durham, NC 27710, USA

Diagnosis

Although the distribution of etiologies for pediatric PH is quite different from that seen in adults, the underlying pathophysiology is similar, and the fundamental diagnostic criteria are nearly identical [7]. A definitive diagnosis of PH is based on demonstration of a resting mean pulmonary arterial pressure

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(mPAP) greater than or equal to 25 mmHg assessed by right heart catheterization [8, 9••]. Pulmonary arterial hypertension (PAH) actually refers to a subgroup of patients with pre-capillary PH, defined as a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and an indexed pulmonary vascular resistance (PVRI) greater than three Wood units × m^2 in the absence of other etiologies (lung disease, chronic thromboembolic pulmonary hypertension, and other rare causes) [9••, 10]. Pediatric PAH is the focus of this review because treatment of post-capillary PH typically depends on identification and correction of the post-capillary etiology (e.g., left heart diastolic dysfunction, mitral stenosis, pulmonary vein stenosis). PAH can be either primary/idiopathic, in the absence of identifiable causes, or secondary, arising from other disease processes. Notably in children, congenital heart disease, primary pulmonary hypertension of the newborn (PPHN), and genetic disorders are major contributors to disease. These diagnoses account for a significantly smaller proportion of cases of PAH in adults.

Evaluation

The evaluation of PAH in pediatric patients requires a comprehensive assessment to confirm the diagnosis, to rule out secondary causes, and to assess disease severity and prognosis. Recent guidelines from the American Heart Association and American Thoracic Society have helped to standardize the diagnostic approach (Fig. 1) [9••].

Obtaining a thorough clinical history and physical exam is paramount. Signs and symptoms of PAH can be subtle and non-specific [11]. Progressive dyspnea on exertion is the most common presenting symptom, but hemoptysis, chest pain, dizziness, syncope, and signs of right heart failure (lower extremity edema, ascites) may all be clinical findings in patients with PAH. Physical exam findings may include a right ventricular lift and accentuation of the pulmonic valve component (P_2) of the second heart sound. Advanced disease is suggested by central cyanosis, digital clubbing, hepatosplenomegaly, ascites, and peripheral edema.

Cardiac catheterization is the "gold standard" for diagnosis of PH [9••]. Catheterization is required to exclude contributing diagnoses such as pulmonary vein stenosis or left heart diastolic dysfunction (i.e., post-capillary PH), to measure intracardiac and pulmonary arterial pressures, and to determine PVRI. Acute vasoreactivity testing, most commonly using inhaled nitric oxide (iNO) and/or 100% oxygen, should be performed unless there is a specific contraindication. Responsiveness to pulmonary vasodilators is used to guide therapy and for prognostication. Following the initiation of therapy, a repeat cardiac catheterization is recommended in 3–12 months to evaluate the patient's response to therapy [9••].

A comprehensive workup also includes identification of secondary, contributing diagnoses. Serologic testing for

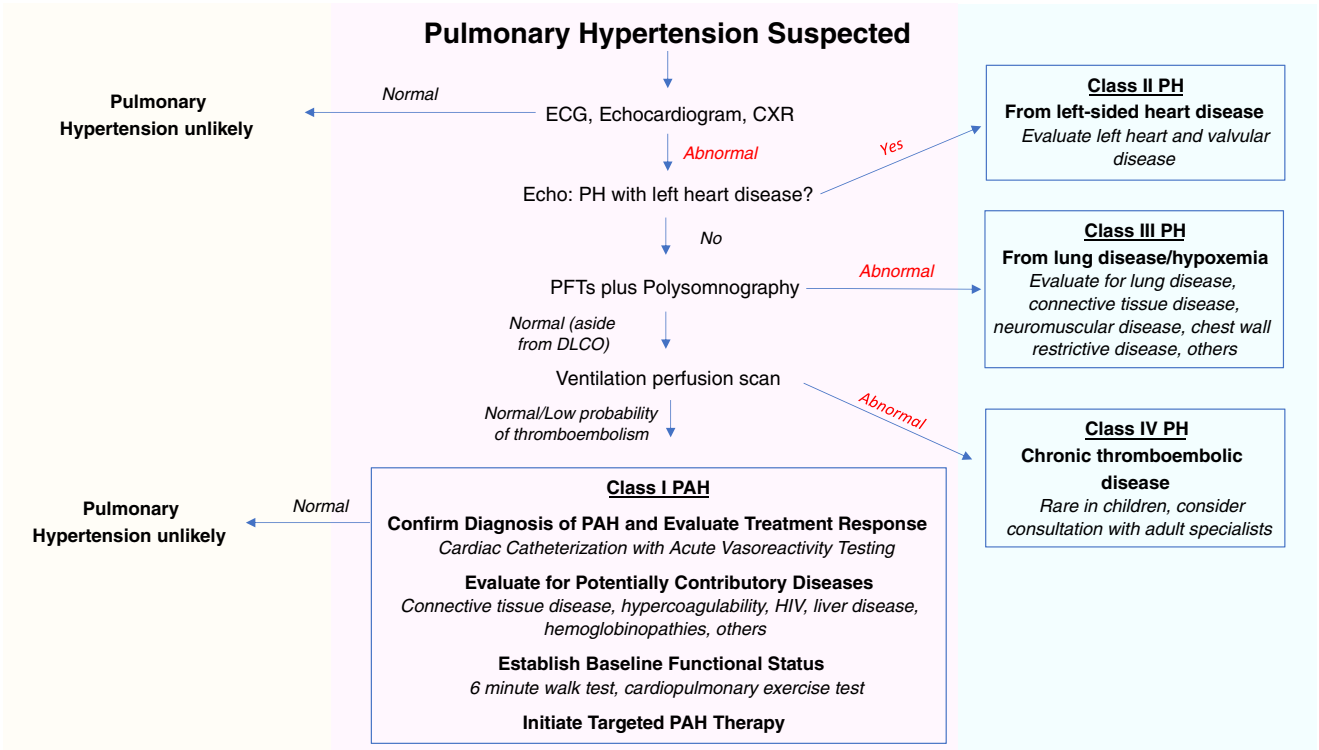

Fig. 1 Diagnostic algorithm detailing the general workup for pediatric pulmonary hypertension. PAH, pulmonary arterial hypertension; DLCO, diffusing capacity of the lung for carbon dioxide; ECG, electrocardiogram; CXR, chest x-ray; PFTs, pulmonary function test. (Source: [9••])

systemic diseases and secondary causes of PAH is recommended in children, including testing for rheumatologic and connective tissue disorders (Fig. 1). Brain natriuretic peptide (BNP) can be followed over time to assist in determining efficacy of treatment. If a strong family history is identified, genetic testing may be useful.

Multiple imaging modalities may be utilized for the work-up of PAH. Chest roentgenogram is useful for ruling out parenchymal lung disease and skeletal anomalies. Echocardiography is a key non-invasive tool for screening for and assessment of PH. In addition to ruling out unrecognized congenital heart disease, echocardiography can assess ventricular function and estimate pulmonary arterial pressures, albeit with less reliability than cardiac catheterization. MRI and CT pulmonary angiography are sometimes useful as supplemental tools for evaluating PAH and associated underlying disorders. Ventilation-perfusion scintigraphy should be performed in patients with suspected idiopathic PAH to exclude chronic thromboembolic disease and in patients with Eisenmenger's syndrome due to the known increased risk of thromboembolism.

Other studies such as cardiopulmonary exercise testing, 6-min walk test, and pulmonary function test may be useful at the time of diagnosis to quantify limitations in exercise capacity and are often useful in tracking response to therapeutic intervention [12]. Though infrequently performed, lung biopsy can be useful in determining irreversibility of disease and in excluding lung parenchymal diseases such as interstitial lung disease where treatment algorithms differ significantly from the treatment of PAH.

Classification of Pulmonary Arterial Hypertension in Children and Adolescents

The classification of PAH has undergone significant revisions, with the focus of classification schemes shifting from assessment of primarily clinical factors to incorporation of histopathologic features and response to therapeutics. Pediatric PAH classification has traditionally been based on adult criteria, which were originally defined by the World Health Organization (WHO) in 1973 [13] and subsequently revised at the World Symposium on Pulmonary Arterial Hypertension meetings in 1998 (Evian) [14], 2003 (Venice) [15], 2008 (Dana Point) [16], and 2013 (Nice) [7]. The most recently published version, the Nice Classification, identifies five categories of PAH, grouped based on shared clinical and pathophysiologic features (Table 1).

Progressive iterations of the PAH classification schemes have increasingly recognized the unique aspects of pediatric PAH. Although pediatric PAH shares the same diagnostic criteria as adult PAH, the distribution of etiologies of pediatric PAH is quite different from adults, with a predominance of idiopathic PAH and PAH associated with congenital heart disease (CHD). The 2013 Nice Classification scheme includes a number of modifications from the previous iteration (the 2008 Dana Point Classification) based on recommendations from the Pediatric Task Force [17] including:

- Addition of novel genetic disorders that cause PAH
- Creation of a separate subcategory within group 1 (1″) to define PPHN
- Addition of congenital and acquired left heart inflow and outflow obstructive lesions to group 2. Lesions included in this group include pulmonary vein stenosis, cor triatriatum, supravalvular mitral ring, mitral stenosis, subaortic stenosis, aortic valve stenosis, and coarctation of the aorta associated with an increased left ventricular end-diastolic pressure
- Recognition of the role of developmental lung diseases, including relatively common entities such as congenital diaphragmatic hernia and bronchopulmonary dysplasia, in group 3
- Addition of segmental PAH, including PAH associated with branch pulmonary artery stenosis or multiple aortopulmonary collaterals to group 5
- Perhaps most importantly, given the relative prevalence of PAH associated with CHD in children, the NICE Classification scheme includes an updated classification for PAH associated with CHD with these lesions classified into four subgroups within type 1 PAH:

    1. Patients with Eisenmenger syndrome
    2. Patients with left to right shunts and elevated PVR but without cyanosis
    3. Patients with PAH and coincidental CHD (e.g., small ASDs and VSDs)
    4. Patients with post-operative PAH

Despite these valuable pediatric modifications, there is recognition that "simplified" modifications of adult PH classification schemes, while valuable for prognostic or treatment stratification, sometimes fail to account for the vast heterogeneity of pediatric PH and in particular PAH associated with CHD. A recent analysis documented that 11% of children with PAH associated with CHD could not be classified into any of the four Nice CHD subgroups [18••]. Other problems include the relatively artificial distinction between subgroups 1 (Eisenmengers) and 2 (left to right shunt lesions) since patients in subgroup 2 progress to subgroup 1 over time, the lack of clear definitions for the "coincidental" CHDs that comprise subgroup 3, and difficulties classifying patients with single ventricle defects where elevated PVRI may contribute to morbidity despite pulmonary arterial pressures that do not meet strict definitions of PAH. Alternative pediatric classification schemes have attempted to address these and other concerns

Table 1 Comparison of the World Health Organization and Panama Pulmonary Hypertension Classification Schemes

WHO classification (NICE)	Panama/PVRI classification
1. Pulmonary arterial hypertension	1. Prenatal or developmental pulmonary hypertensive vascular disease
1.1 Idiopathic PAH	1.1 Associated with maternal or placental abnormalities
1.2 Heritable PAH	1.2. Associated with fetal pulmonary vascular maldevelopment
1.2.1 BMPR2	1.3 Associated with fetal cardiac maldevelopment
1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3	2. Perinatal pulmonary vascular maladaptation (persistent pulmonary hypertension of the neonate, PPHN)
1.2.3 Unknown	2.1 Idiopathic PPHN
1.3 Drug and toxin induced	2.2 PPHN associated with or triggered by sepsis, meconium aspiration, CHD, CDH, trisomy (13, 18, 21), drugs, and toxins
1.4 Associated with:	3. Pediatric heart disease
1.4.1 Connective tissue disease	3.1 Systemic to pulmonary shunts
1.4.2 HIV infection	3.1.1 PAH associated with systemic to pulmonary shunt with increased PVRI, no R-L shunt
1.4.3 Portal hypertension	3.1.2 Classical Eisenmenger syndrome
1.4.4 CHD	3.1.2.1 Eisenmenger–simple lesion (ASD, VSD, PDA)
1.4.5 Schistosomiasis	3.1.2.2 Eisenmenger–complex lesion (Truncus, TGA/VSD, single ventricle)
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	3.1.3 Small defect with elevated pulmonary arterial pressure/PVRI out of proportion to the size of the defect
1.1″ PPHN	Coexistent with pulmonary hypoplasia
2. Pulmonary hypertension due to left-sided heart disease	Coexistent with inherited or idiopathic pulmonary hypertensive vascular disease
2.1 LV systolic dysfunction	3.2 Post-operative pulmonary arterial hypertension following
2.2 LV diastolic dysfunction	3.2.1 Closure of shunt with
2.3 Valvular disease	3.2.1.1 Persistent increase in PVRI > 3 WU·m^2
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	3.2.1.2 Recurrent increase in PVRI > 3 WU·m^2
3. Pulmonary hypertension caused by lung disease and/or hypoxia	3.2.2 Arterial or atrial switch operation for TGA with intact ventricular septum
3.1 Chronic obstructive pulmonary disease	3.2.3 Repair of left heart obstruction
3.2 Interstitial lung disease	3.2.4 Repair of tetralogy of Fallot
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern	3.2.5 Repair of pulmonary atresia with VSD and MAPCA's
3.4 Sleep-disordered breathing	3.2.6 Surgical aortopulmonary shunt
3.5 Alveolar hypoventilation syndromes	3.3 Pulmonary vascular disease following staged palliation for single ventricle physiology
3.6 Long-term exposure to high altitudes	3.3.1 After stage 1 (PA banding, modified Norwood, hybrid procedure, aortopulmonary or ventricular pulmonary shunt, stenting PDA)
3.7 Developmental lung diseases	3.3.2 After SVC to PA anastomosis (Glenn)
4. Chronic thromboembolic disease (CTEPH)	3.3.3 After total cavopulmonary anastomosis (Fontan)
5. Pulmonary hypertension with unclear or multifactorial mechanisms	3.4 Pediatric pulmonary hypertensive vascular disease associated with congenital abnormalities of the pulmonary arteries/veins
5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy	3.4.1 PPHVD associated with congenital abnormalities of the pulmonary arteries
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis	3.4.1.1 Origin of a pulmonary artery from the aorta
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders	3.4.1.2 Unilateral isolation/ductal origin/"absence" of a pulmonary artery
5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension	3.4.2 PPHVD associated with congenital abnormalities of the pulmonary veins
	3.4.2.1 Scimitar complex
	3.4.2.2 Pulmonary vein stenosis
	3.4.2.3 Cantú syndrome
	3.5. Pulmonary venous hypertension
	3.5.1. Pulmonary venous hypertension due to congenital left heart inflow or outflow disease: aortic stenosis, aortic incompetence, mitral stenosis, mitral regurgitation, supramitral ring, pulmonary vein obstruction, cor triatriatum, endocardial fibroelastosis, left ventricular hypoplasia/Shone's complex, congenital cardiomyopathy, restrictive atrial septum in hypoplastic left heart syndrome
	3.5.2. Pulmonary venous hypertension due to acquired left heart disease
	Left-sided valvar heart disease (rheumatic/postendocarditis/rheumatoid arthritis)
	Restrictive /dilated /hypertrophic cardiomyopathy
	Constrictive pericardial disease
	4. Bronchopulmonary dysplasia
	5. Isolated pediatric pulmonary hypertensive vascular disease (PPHVD) or isolated pulmonary arterial hypertension (PAH)
	5.1 Idiopathic PPHVD/idiopathic PAH
	5.2 Inherited PPHVD/PAH (BMPR2, Alk 1, endoglin, or unidentified genetic cause)
	5.3 Drugs and toxins
	5.4 Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (idiopathic or inherited)
	6. Multifactorial pulmonary hypertensive vascular disease associated with multiple congenital malformations/syndromes. Syndromes with and without CHD may include: VACTERL, CHARGE, Poland, Adams-Oliver syndrome, Scimitar complex, trisomy, Di George, Noonan, Von Recklinghausen disease, Dursun syndrome, Cantú syndrome
	7. Pediatric lung disease
	7.1 Cystic fibrosis
	7.2 Interstitial lung diseases: surfactant protein deficiency, etc.
	7.3 Sleep-disordered breathing
	7.4 Chest wall and spinal deformities
	7.5 Restrictive lung diseases
	7.6 Chronic obstructive lung diseases
	8. Pediatric thrombo-embolic disease causing pulmonary hypertensive vascular disease
	9. Hypobaric hypoxic exposure
	10. Pulmonary hypertensive vascular disease associated with other system disorders
	10.1 Pediatric portal hypertension
	10.2 Pediatric hematological disease
	10.3 Pediatric oncological disease
	10.4 Pediatric metabolic/endocrine disease
	10.5 Pediatric autoimmune or autoinflammatory disease
	10.6 Pediatric infectious disease
	10.7 Pediatric chronic renal failure

WHO World Health Organization, *PVRI* Pulmonary Vascular Research Institute

unique to pediatric patients; the Pulmonary Vascular Research Institute (PVRI) developed a unique pediatric classification known as the Panama criteria [12, 19] (Table 1). This classification system emphasizes elevated PVRI as a more specific classification criterion than pulmonary arterial pressures alone and addresses factors such as perinatal maladaptation, developmental defects, and pulmonary hypoplasia.

Treatment of PAH in Children and Adolescents

Pediatric treatment algorithms for PAH are almost all derived by extrapolating safety and efficacy from the adult PAH literature. Extrapolation is necessary because very few targeted PAH therapies have been rigorously studied in children; therefore, most of these therapies do not have either a US Food and Drug Administration (FDA) or a European Medicines Agency (EMA)–approved indication for pediatric use and instead must be used "off-label." This is suboptimal as pediatric patients with PAH may differ from adults in their response to therapies [20–22]. Nonetheless, off-label treatment is not unusual in children with complex diseases [23] and given the poor prognosis represents a preferred alternative to no treatment at all. Table 2 outlines therapeutic options for treatment of pediatric PAH and provides commonly used dosing ranges.

Background Therapies

For all patients with pediatric PAH, the AHA guidelines provide a Class IIb recommendation of supportive care with oral heart failure therapies and diuretics in patients with signs of right heart failure [9••]. Anticoagulation with warfarin targeting an international normalized ratio between 1.5 and 2.0 is recommended for older children with poor cardiac output, indwelling lines, or predisposition to hypercoagulability. Anticoagulation is not recommended for young children due to the risk of hemorrhagic complications. Oxygen therapy may be initiated as an adjunct therapy for cyanotic patients with oxygen saturations < 92%, particularly if respiratory disease is the underlying etiology of PAH.

Inhaled Nitric Oxide

Nitric oxide (NO) is endogenously produced by endothelial nitric oxide synthase in vascular endothelial cells and acts on vascular smooth muscle to increase intracellular concentrations of cGMP which decreases vascular smooth muscle tone. Additionally, NO plays a role in vascular remodeling including proliferation, apoptosis, and angiogenesis [24]. When administered via aerosolized inhalation, NO crosses the alveolar-capillary membrane to enter the smooth muscles of the pre-capillary pulmonary arterioles, causing selective vasodilation and attenuation of vascular remodeling [25].

Inhaled nitric oxide (iNO) is approved by the FDA for use in newborns with PPHN. Multicenter trials from the Pediatric Pulmonary Hypertension Network have shown a reduction in the need for ECMO when iNO is used in the management of PPHN [26]. It is routinely used for acute vasoreactivity testing in the catheterization laboratory and is often used following repair of congenital diaphragmatic hernias or congenital heart disease.

iNO is rapidly metabolized and inactivated and has a short half-life of 15–30 s. Its rapid metabolism prevents systemic distribution, making iNO a highly selective therapy for PAH. Patients receiving long-term, high-dose iNO should be monitored for nitrogen dioxide (NO_2) and methemoglobinemia. A dose range of 5–40 ppm is considered to provide optimal therapeutic effect with a low risk of side effects [27, 28].

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE5) is an enzyme expressed in lung and penile tissue which degrades cGMP causing vasoconstriction of smooth muscle. PDE5 is upregulated in PAH causing an exaggerated vasoconstriction effect. PDE5 inhibitors induce pulmonary vasodilation by blocking the effect of PDE5, thereby increasing the concentration of intracellular cGMP in the pulmonary vasculature and promoting smooth muscle relaxation. This increase in cGMP has also been found to have antiproliferative and proapoptotic effects [29, 30].

PDE-5 inhibitors have been used as first-line therapy for children with PAH for decades [31, 32]. Treatment with PDE-5 inhibitors has been associated with improvements in PVR and cardiac contractility, yielding improved exercise performance and patient-reported quality of life measures [33–35]. Furthermore, preliminary studies suggest that these agents may also have some ventricular remodeling properties [31, 36].

Sildenafil (Revatio) is a PDE5 inhibitor which is frequently used in the pediatric population and is approved for the treatment of pediatric PAH in Europe. Data from the Sildenafil in Treatment-Naïve Children, Aged 1–17 years, with Pulmonary Arterial Hypertension trials (STARTS-1 and STARTS-2) demonstrate that sildenafil improves peak oxygen consumption, functional class, and hemodynamics and is well tolerated in medium weight-based doses (approximately 0.5–1 mg/kg) [37]. However, the STARTS-2 trial found an unexpected increase in mortality in the high-dose group on follow-up at 3 years [6, 37]. In response to these results, an FDA warning was issued regarding use of sildenafil in children. These results remain controversial; an expert consensus statement from the Pediatric Pulmonary Hypertension Network released in response to the FDA warning recommended continued use

Table 2 Medication options for pediatric PAH

Medication class	Medication	Route	Dose/titration	Adverse effects
Nitric oxide	Nitric oxide	Inhalation	5–40 ppm	Methemoglobinemia
Phosphodiesterase-5 inhibitors	Sildenafil (Revatio)	Oral	Initial, 0.5–1 mg/kg/dose TID Maintenance, 1–2 mg/kg/dose TID *Adult dose, 20 mg PO TID*	Headache, flushing, nasal congestion, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, back pain, sensorineural hearing loss, ischemic optic neuropathy, priapism
		IV	Loading, 0.4 mg/kg over 3 h Continuous infusion, 1.6 mg/kg/day	Avoid nitrates Delay use in extremely preterm infants until retinal vascularization is established
	Tadalafil (Adcirca)	Oral	0.5–1 mg/kg/dose daily *Adult dose, 40 mg daily*	Similar to sildenafil Co-administration with nitrates is contraindicated
Endothelin receptor antagonists	Bosentan (Tracleer)	Oral	2 mg/kg/dose BID 10–20 kg, 31.25 mg BID 20–40 kg, 62.5 mg BID > 40 kg, 125 mg BID *Adult dose:* *- Initial 62.5 mg BID* *- Maintenance 125 mg BID*	Abdominal pain, vomiting, fatigue, headache, edema, flushing, nasal congestion, anemia, decreased sperm count Risk of dose-related increases in liver enzymes Contraindicated in hepatic impairment (monitoring required) Caution with concomitant CYP3A4 inducers and inhibitors Teratogenic
	Ambrisentan (Letairis)	Oral	< 20 kg, 2.5–5 mg daily > 20 kg, 5–10 mg daily *Adult dose:* *- Initial 5 mg daily* *- Maintenance 10 mg daily*	Similar to bosentan Lower risk of liver enzyme elevation Teratogenic
	Macitentan (Opsumit)	Oral	10 mg daily	Similar to bosentan Lower risk of liver enzyme elevation Teratogenic
Prostacyclins	Epoprostinol (Flolan, Veletri)	IV	Initial, 1–3 ng/kg/min Maintenance, 50–80 ng/kg/min	Nausea, flushing, headache, diarrhea, rash, jaw discomfort, thrombocytopenia Hypotension and bleeding with concomitant use of anticoagulants, platelet inhibitors, or vasodilators
	Iloprost (Ventavis)	Inhaled	Initial, 2.5 μg 6 times per day Maintenance, 5 μg 9 times per day	Cough, wheeze, flushing, headache, jaw pain, diarrhea, rash, hypotension May exacerbate reactive airways disease
	Treprostinil (Remodulin, Tyvaso, Orenitram)	IV/subcutaneous	Initial, 1.25–2 ng/kg/min Maintenance, 50–80 ng/kg/min	Flushing, headache, nausea, diarrhea, musculoskeletal pain, rash, hypotension, thrombocytopenia, hypokalemia, pain at injection site
		Oral	Initial, 0.25 mg BID Maintenance, determined by tolerability	Hypotension and bleeding with concomitant use of anticoagulants, platelet inhibitors, or vasodilators
		Inhaled	Initial, 18 μg QID	May exacerbate reactive airways disease at higher doses
Soluble guanylate cyclase stimulator	Riociguat (Adempas)	Oral	Initial, 0.5-1 mg TID Maintenance, 2.5 mg TID	Headache, dizziness, dyspepsia, nausea, diarrhea, anemia, hypotension, vomiting, gastrointestinal reflux, constipation Co-administration with nitrates and/or PDE-5 inhibitors is contraindicated Teratogenic

IV intravenous, *SC* subcutaneous, *BID* 2 times per day, *TID* 3 times per day, *QID* 4 times per day

of sildenafil with avoidance of high doses [38]. In 2014, the FDA clarified its previous warning by stating, "the risks and benefits of sildenafil should be considered when treating pediatric patients with pulmonary hypertension."

Despite the FDA warning, sildenafil is used by many providers as first-line therapy for PAH treatment in children due to the ease of oral dosing and the fact that there is no need for blood monitoring (in contrast to endothelin receptor antagonists [ERAs], see below). Sildenafil is generally well tolerated. It is rapidly absorbed and reaches peak concentration in 1–2 h with a relatively short half-life of approximately 4 h. This necessitates frequent dosing, approximately every 6–8 h, to maintain steady state. Sildenafil is metabolized in the liver by the cytochrome P450 CYP34A enzyme, and doses must be roughly doubled when co-administered with bosentan, a potent CYP3A4 inducer. An oral sildenafil dose of 0.5 to 1 mg/kg (approximating the medium dose range in the STARTS trials) is routinely targeted to achieve efficacy and minimize side effects. Intravenous sildenafil may be considered in critically ill pediatric patients unable to tolerate oral medications, with targeted doses of approximately half the oral dosage [39–41].

Tadalafil (Adcirca) is a long-acting PDE5 inhibitor. Like sildenafil, tadalafil is also well tolerated; however, its longer half-life enables daily dosing, as opposed to the more frequent dosing required for sildenafil. Tadalafil reaches peak concentrations at 2 h and has a half-life of 35 h after oral administration based on adult studies [42]. Steady-state concentrations are achieved in approximately 5 days following initiation at 20 mg or 40 mg daily. The use and tolerability of tadalafil has not been described in children less than 4 years of age, and due to the immaturity of the glucuronidation pathway, tadalafil is contraindicated in neonates.

Udenafil (Zydena), a new long-acting PDE5 inhibitor, is currently being investigated in the pediatric population for use in patients who have previously undergone the Fontan procedure. A phase I/II trial conducted by the Pediatric Heart Network Investigators found that short-term administration of udenafil to adolescents with Fontan physiology was well tolerated at all dosing levels, and the results suggested udenafil may improve myocardial performance. Currently, the PHN investigators are conducting the Fontan Udenafil Exercise Longitudinal (FUEL) Trial to evaluate the long-term efficacy of udenafil in Fontan patients [43]. An extension of the trial, the FUEL Open-Label Extension (FUEL-OLE), will be conducted following completion to further evaluate safety and tolerability.

With all PDE5 inhibitors, patients must be monitored for adverse effects. The most common are headache, flushing, and dizziness. Serious hearing and visual defects have been reported in adult patients. Patients with CrCL < 30 ml/min or cirrhosis may require a dose reduction [44]. PDE5 inhibitors should not be used with nitrates due to the risk of life-threatening hypotension. Erections can occur in approximately 10% of boys.

Endothelin Receptor Antagonists

ERAs target the endothelin signaling pathway by inhibiting binding of endothelin-1, a potent vasoconstrictor peptide, to its G-protein-coupled receptors, endothelin type A and type B, on endothelial cells in the pulmonary vasculature. Endothelin type A receptors constrict blood vessels by increasing intracellular calcium concentration while endothelin type B receptors cause vascular relaxation by stimulating the release of NO and prostaglandins while also inhibiting vascular proliferation and potentiating remodeling [45].

Bosentan (Tracleer) is a non-selective ERA, targeting both type A and type B endothelin receptors. Bosentan improves exercise capacity and hemodynamics in adults with PAH [46]. It is available as a tablet and can be crushed and compounded into a liquid suspension. Bosentan has a short half-life of approximately 5 h and requires twice-daily dosing. Bosentan is a potent CYP3A4 inducer, and dosing of other drugs metabolized by the CYP3A4 enzyme (e.g., sildenafil) must be adjusted when administered in combination with bosentan. Bosentan can cause elevation of hepatic aminotransferases and cases of hepatic cirrhosis have been reported with chronic use. Therefore, monthly monitoring of aminotransferases is recommended in all patients taking bosentan. Discontinuation usually leads to normalization of liver enzymes over time.

Ambrisentan (Leiteris) is a selective ERA, targeting type A endothelin receptors only. Ambrisentan has a half-life of approximately 9 h and requires once-daily dosing. Ambrisentan does not have the same propensity for hepatotoxicity as bosentan, and therefore, liver enzymes do not need to be checked. A drawback for ambrisentan use in children is the fact that it is a highly hydrophobic drug and is therefore difficult to compound in an oral suspension. In two multicenter adult trials (ARIES-1 and ARIES-2), ambrisentan was found to significantly improve performance on the 6-min walk test when compared with placebo [47].

Macitentan (Opsumit) is a non-selective ERA, targeting both type A and type B endothelin receptors; however, macitentan has a stronger affinity for type A receptor antagonism. The SERAPHIN trial assessed efficacy of long-term macitentan therapy compared with placebo and found that treatment with macitentan was associated with significant reductions in morbidity and mortality among adult patients with PAH [48]. The TOMORROW trial (ClinicalTrials.gov NCT02932410) is a multicenter, multinational, randomized controlled trial that is currently enrolling and aims to assess safety, efficacy, and pharmacokinetics of macitentan in comparison with standard of care in children ages ≥ 2 to < 18 years with PAH [49].

Both ambrisentan and bosentan are commonly used in children, although use of these drugs is "off-label." Ambrisentan is generally preferred in older children due to its reduced risk of

hepatotoxity, while bosentan is preferred in younger children because it can be more easily compounded in an oral suspension. There is hope that completion of the TOMORROW trial might provide the first labeled indication for an ERA in children. A major concern with the use of all ERAs is that they are potentially teratogenic (pregnancy category X). ERAs should not be taken by women who are pregnant or who wish to become pregnant, and a baseline pregnancy test is recommended before initiation of therapy in all females of childbearing age.

Prostanoids

Prostanoids, such as prostacyclin, are produced endogenously from arachidonic acid in the vascular endothelium and have significant effects on the vasculature including vasodilation, antiproliferation, antithrombosis, and anti-inflammatory properties. Prostacyclin effects are mediated by G-protein receptors on the surface of pulmonary endothelial cells or platelets and by increased intracellular cAMP leading to smooth muscle relaxation. Prostacyclin synthase and metabolites of prostacyclin are decreased in PAH resulting in a lower level of prostacyclin.

Prostacyclins are FDA-approved in adults and are used "off-label" in children who fail to improve on other therapies or those who are at higher baseline risk at the time of diagnosis. Intravenous, inhaled, subcutaneous, and oral formulations are available.

Epoprostenol (Flolan, Veletri) has a rapid onset of action, reaching steady state in approximately 15 min and has a short half-life. It is therefore administered via continuous IV infusion. It has been shown to improve exercise tolerance and survival in adult patients with PAH [50, 51]. In children, it improves hemodynamics, symptoms, and survival in patients with idiopathic PAH and PAH secondary to CHD [52]. Inhaled epoprostenol has been successfully used in place of iNO in critical care settings.

Patients being treated with epoprostenol should be monitored for adverse effects, particularly at initiation including bradycardia, hypotension, and thrombocytopenia. Caution should be used when administering epoprostenol to patients with parenchymal lung disease, as it can worsen ventilation-perfusion matching. Epoprostenol can also cause life-threatening pulmonary edema in patients with PAH secondary to veno-occlusive disease or pulmonary vein stenosis. Since epoprostenol affects G-protein receptors on both the pulmonary endothelium and platelets, platelet function (aggregation) can be adversely affected, conferring an increased risk of bleeding, particularly in patients also treated with anticoagulant agents. Care should also be taken when discontinuing therapy, as acute discontinuation can cause rebound pulmonary hypertension.

Iloprost (Ventavis) is an inhaled analogue of prostacyclin, which reaches steady state in approximately 5–10 min with a half-life of 20–25 min. It is predominantly cleared by the kidneys; therefore, dose adjustments in renal disease may be prudent. Iloprost does not induce systemic hypotension [53], unlike other agents in the prostanoid class; and there are no significant interactions with other pulmonary vasodilator agents. The use of iloprost has been shown to improve functional status in children with idiopathic PAH and PAH from CHD [54]. Additionally, iloprost has been successfully used as an alternative to iNO in the post-operative period following congenital heart surgery [53].

Treprostinil, available in intravenous (Remodulin), subcutaneous (Remodulin), oral (orenitram), and inhaled (Tyvaso) formulations, has a more favorable side effect profile than the aforementioned prostanoid agents. Though no formulation is approved for use in children, multiple studies have demonstrated safety with IV, subcutaneous, and inhaled preparations [55, 56•, 57]. Subcutaneous treprostinil is the most commonly used systemic preparation in children, as it reduces the infectious risk of indwelling intravenous lines and the potential risk of paradoxical air or thromboembolism in patients with unrepaired shunt lesions. The most troublesome side effect is pain and reaction at the infusion site. For IV and subcutaneous formulations, steady state is achieved in approximately 10 h and complete clearance occurs in approximately 4.5 h. Inhaled treprostinil achieves lower plasma concentrations than systemic administration; therefore, patients requiring parenteral treprostinil rates greater than 15 ng/kg/min should not be treated with inhaled treprostanil. Inhaled treprostinil is administered every 4–6 h. Peak levels are reached within 5–10 min of administration. It has few systemic effects and therefore may be initiated or titrated in the outpatient setting. Although a tablet formulation of treprostinil is approved for use in adults, efficacy is lower than the systemically administered preparations due to reduced bioavailability. There have been no published studies examining the safety of oral formulations in children, and the dosing range has not been established. The tablet cannot be crushed and there is no suspension available; therefore, the prospect for its use in younger children is currently limited.

Treprostinil is cleared by the liver; therefore, clearance is decreased in patients with liver disease. Co-administration with ERAs or PDE5 is considered safe; however, administration with anticoagulants or other vasodilators may increase the risk of bleeding and systemic hypotension [58].

Soluble Guanylate Cyclase Stimulators

The soluble guanylate cyclase stimulator, riociguat (Adempas), has a similar mechanism to PDE5 inhibitors in that it increases intracellular cGMP, which results in

vasodilation. Additionally, riociguat directly stimulates soluble guanylate cyclase and increases its sensitivity to nitric oxide. In the CHEST-1 trial, riociguat was found to improve PVR and exercise capacity in adult patients with chronic thromboembolic PH [59]. There are no available data on safety, efficacy, or dosing in children.

Combination Therapy

In the adult literature, there is evidence to suggest synergistic effect when combining agents from different classes to treat PAH [30, 31]. Therefore, many providers target dual agent therapy for patients with moderate PAH and triple drug therapy is used in patients with severe disease. Similar approaches are used in children with PAH.

Surgical Therapies

Children who fail conventional medical therapies might be candidates for palliative surgical procedures such as the Potts shunt (side to side anastomosis between left pulmonary artery and descending aorta), which allows for right heart decompression. Lung transplantation has poor outcomes in children and is considered a treatment of last resort for those who have failed maximal therapy.

Conclusion

PH and more specifically PAH remain a significant source of morbidity and mortality in children. Though there are features common to both adult and pediatric PAH, PAH in infants and children is a distinct entity with a higher proportion of patients having a history of developmental or congenital defects. Pediatric PAH requires targeted therapeutics, and there are increasingly more therapeutic options available to patients with pediatric PAH for "off-label" use. Despite this, there is a need for further investigation of therapies and in particular dosing, safety, and efficacy trials that are targeted to the pediatric population.

Compliance with Ethical Standards

Conflict of Interest Jordan E. Ezekian declares no conflict of interest.

Kevin D. Hill reports another from Actelion (he is a site PI for a multicenter trial of macitentan for treatment of PAH in children).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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