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REVIEW

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An update on the diagnosis and treatment of pediatric pulmonary hypertension

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ABSTRACT

Introduction: Pulmonary hypertension (PH) is a heterogeneous disease that mainly affects the pulmonary arterioles, leading to significant morbidity and mortality. Pulmonary hypertension in children from birth to adolescence presents important differences from that of adults. The majority of pediatric pulmonary arterial hypertension (PAH) cases are idiopathic or associated with congenital heart disease. However, the management of pediatric PAH mainly depends on the results of evidence-based adult studies and the clinical experiences of pediatric experts.

Areas covered: This article briefly reviews the recent updates on the definition, classification, and diagnostic evaluation of pediatric PAH and their impact on treatment strategies. The main purpose of this review is to discuss the current pediatric therapies, as well as the prospective therapies, in terms of therapeutic targets, actions, side effects, and dosages.

Expert opinion: Although there is no cure for PAH, recent advances in the form of new treatment options have improved the quality of life and survival rates of PAH patients. PAH-targeted drugs and treatment strategies for adult PAH have not been sufficiently studied in children. However, the growing scientific activity in that field will surely change the treatment option recommendations in pediatric PH from experience-based to evidence-based in the near future.

ARTICLE HISTORY

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KEYWORDS

Children; new treatment targets; pediatrics; pharmacotherapies; pulmonary arterial hypertension; guidelines for therapy

1. Introduction

Pulmonary hypertension (PH) is a rare and progressive disease characterized by elevated levels of pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), right ventricular dysfunction, and terminal heart failure. Various etiological factors can trigger this disease in children, however, regardless of the etiology, most of the cases present with a poor prognosis [1,2]. The median survival rates for patients with idiopathic pulmonary arterial hypertension (IPAH) were 10 months and 2.8 years in children and adults, respectively, [3]. Pediatric pulmonary arterial hypertension (PAH) exhibits differences and similarities compared to adult PAH [1,4]. A unique pediatric PAH profile was first considered at the 2013 World Symposium on Pulmonary Hypertension (WSPH) [3,5] and updated with a new definition and a revised classification at the 2018 WSPH [6,7]. The detailed etiological classification and diagnostic algorithms have enabled the physicians to conduct more accurate diagnoses and better risk stratification and to initiate PAH-targeted therapies in early stages in pediatric patients [8].

Recent advances in new treatment modalities, such as early initiation, upfront combination, and targeted drugs, have improved the prognosis and quality of life (QOL) of PAH patients [9]. However, the treatment of pediatric PAH remains challenging because to date these treatments have been dependent on evidence-based adult studies and pediatric expert opinions [10]. Despite the lack of randomized clinical trials (RCTs), we know that children with PAH benefit from treatment with PAH-targeted drugs based on the extensive supporting data on pediatric PAH treatment [2,5,8,10].

This review briefly discusses the recent advances in the definition, classification, risk stratification, and treatment modalities of PAH in children. Future therapeutic options, as well as current therapies for pediatric PAH patients, are also highlighted with a special emphasis on the challenges and distinct properties of treating children with PAH.

2. Definition and classification

2.1. Definition

PAH is defined as mean 'pulmonary artery pressure (mPAP) greater than 25 mm Hg at rest, pulmonary vascular resistance (PVR) greater than 3 woods units m2, and pulmonary arterial wedge pressure (PAWP) less than 15 mm Hg.' This definition is accepted for adults and children since 1973 (1st.WSPH in Geneva) [11]. In the 6th.WSPH, the cut off value for the normal mPAP changed to 20 mm Hg, based on the data reported by Kovacs et al. [12]. In their review on 1,187 healthy subjects, right heart catheterization (RHC) studies showed that the normal mPAP was 14.0 ± 3.3 mmHg at rest. Considering two standard deviations, mPAP of = 20 mm Hg was suggested as the upper limit for normal adults; their findings were supported by Maron et al. [13]. For consistency, the Pediatric Task Force of the 6th.WSPH decided to use the new definition of PAH in children as well [6].(Table 1)

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Article highlights

- · Pulmonary hypertension is a rare and progressive disease
- New definition, revised classification, and updated risk variables are important in diagnosis and follow-up of pediatric PH
- Pediatric PAH exhibits similarities and differences compared to adult PAH.
- Recent advances in drug therapies and new treatment strategies such as early initiation, upfront combination have improved the QOL and survival rates in children with PAH
- · Novel therapeutic targets and drugs are needed

The growing number of scientific reports regarding pediatric PAH warrant that the existing knowledge on the treatment strategy of this rare disease could improve.

This box summarizes the key points contained in the article.

In small children, whose normal systemic arterial pressure (SAP) is low, the ratio of mPAP to mean systemic arterial pressure (mSAP) can be used to describe the severity of the PAH. However, these definitions are still arbitrary for children because of limited pediatric data on the normal hemodynamic values and their impact on the prognosis [14]. Furthermore, single ventricle circulation is an exception to this definition; in Fontan patients, mPAP above 15 mm Hg or even a very mild elevation in mPAP can lead to Fontan failure and circulatory collapse.

2.2. Classification

An updated and simplified version of the clinical classification of PH was proposed and accepted at the 6th WSPH (Table 2) [7]. In this classification, a new subgroup was added to group 1, 'Long-term responders to calcium channel blockers. This group was, first by Rich et al. [15] and then by Sitbon et al. [16] reported to exhibit a positive response in the acute vasoreactivity test (AVT) and long-term improvement in the clinical course when treated with calcium channel blockers (CCBs). Recently Hemnes et al. showed that AVT responders exhibited different gene variants and specific blood

 Table 1. Definition of pulmonary hypertension. According to 6th. WSPH (Nice 2018)

1. Pulmonary Arterial Hypertension (PAH)
mPAP > 20 mm Hg
$PAWP \leq 15 mm Hg$
PVR index \geq 3WUm ²
2. Pre- capillary Pulmonary hypertension (PH)
mPAP > 20 mm Hg
PAWP or LVEDP \leq 15 mm Hg
PVR index \geq 3WUm ²
Diastolic TPG > 7mmHg
3. Post Capillary Pulmonary hypertension
mPAP > 20 mm Hg
PAWP or LVEDP \geq 15 mm Hg
PVR index \leq 3 WUm ²
Diastolic TPG < 7mmHg

PAP: pulmonary artery pressure; PAWP: pulmonary artery

wedge pressure; PVR: pulmonary vascular resistance. TPG.trans pulmonary gradient

Adapted from [7] with permission of the European Respiratory Society.

Table 2. Clinical classification of PH (6 WSPH updated version).

1. Pulmonary arterial hypertension (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 CCBs
- 1.6. PAH with overt features of venous capillaries (PVOD/PCH) involvement*

1.7. Persistent PH of the newborn (PPHN)*

- 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
- 2.3. valvular neart disease
- 2.4. Congenital / acquired cardiovascular conditions leading to post-capillary 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
- 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. Others5.4. Complex congenital heart disease*

5.4. complex congenital neart discuse

*Prevalent mostly in children and need sub-classification. CCB: calcium channel blocker; PVCD: pulmonary veno-oclusive disease; PCH: pulmonary capillary hemangiomatosis; LVEF: left ventricular ejection fraction.

Reproduced from [7] with the permission of the European Respiratory Society.

characteristics, which differentiated them from other PH groups [17,18]. It has been reported that around 8–15% of children with IPAH belong to this group [7].

The new classification was primarily based on pathological and etiological features and partly based on clinical presentation and treatment modalities. Pediatric PAH needs to be subclassified on the basis of specific conditions, such as congenital heart disease (CHD), congenital lung disease, and a persistent PH of newborns (PPHN) [6,19]. For example, PAH-CHD is classified as; Eisenmenger syndrome, operable and inoperable left-to-right shunts, coincidental defects, and postoperative defects. PPHN is associated with multiple disorders and antenatal and perinatal events. It is the most common cause of transient PAH. Developmental lung disorders include bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia, alveolar capillary dysplasia, surfactant abnormalities, lung hypoplasia, and Down syndrome.

2.3. Epidemiology

PH is a rare, heterogeneous disease. Epidemiological data on pediatric PH is mainly derived from registry cohorts; hence, the level of evidence (LOE) is B or C. Data collected from registries is affected by study designs, inclusion criteria, and diagnostic differences between the registries. The estimated incidence of PH in all categories was reported as 4–10 cases per million children per year with a prevalence of 20–40 cases per million in Europe [20–22] and an incidence of 5–8, with

a prevalence of 26–33 children was reported in the United States (US) [23]. Von Loon et al. reported the annual incidence of pediatric PH as 63.7 per million children. Two-thirds of the cases were transient PH, such as the PPHN and repairable congenital heart defects. Early diagnosis and therapy is important for this group. Among the remaining pediatric cases, 34% had PH due to lung diseases and, 27% had other forms of PAH, such as IPAH, PAH-CHD, and PAH associated with connective tissue disease (PAH-CTD), and pulmonary veno-occlusive disease (PVOD) [21]. In the French registry, the prevalence of PH in children was 3.7 cases/million, 60% of which was classified as IPAH, 10% as hereditary PAH (HPAH), and 24% as PAH-CHD, while 4% and 2% were classified as PAH-CTD and portal hypertension, respectively, [24].

3. Diagnostic tests

Accurate diagnosis of PH is extremely difficult because of the diversity of etiological factors. Many registries show that most pediatric patients do not undergo complete evaluations [2–4,14,24]. Hence, simple and more convenient diagnostic algorithms are needed. PH diagnosis commences with the suspicion of PH followed by a comprehensive history and physical examination. ECG, CXR, transthoracic echocardiography (TTE), and pulmonary function tests (PFTs) including DLCO must be performed in the first step. If PH is not confirmed, we must consider other pathologies; however, if PH suspicion is confirmed, the child must be referred to a PH center for advanced evaluation, risk stratification, and treatment [6,14,20] (Figure 1).

TTE is important for the evaluation of suspected or confirmed PH patients. An echocardiogram enables the analysis of the cardiac anatomy, ventricular size and function, valve morphology and function, congenital cardiac malformations, and pericardial effusions. TTE evaluations in pediatric PH must follow the multiparametric approach. Parameters, such as RA and RV enlargement, increased RV/LV ratio, and reduced TAPSE, are associated with the prognosis [2,6,14]. Normal TAPSE values in children have been published and can be used as a reference [25]. Doppler examination of tricuspid valve regurgitation flow velocity can be used to determine right ventricle systolic pressure. Pulmonary valve regurgitation jet estimates, PA mean, and end-diastolic pressure. In the absence of measurable tricuspid regurgitation velocity, the pulmonary arterial flow velocity curve can be used to estimate mPAP and PVR [26]. Tissue Doppler imaging (TDI) can be used to determine myocardial velocities, showing RV and LV systolic and diastolic functions. The size ratio of the right ventricle to the left ventricle at the end-systole is accepted as a strong predictor of prognosis [27]. TTE does not establish a definite diagnosis; the PH diagnosis must be confirmed by cardiac catheterization (CC) before the initiation of PH pharmacotherapy.

Cardiac catheterization is the most valuable diagnostic method for the evaluation and classification of PH patients. It is essential for all PH patients except infants with PPHN and BPD and high-risk babies. CC confirms the PH diagnosis; quantifies any shunt lesions; measures the pressures in the right and left heart chamber and vascular structures, the transpulmonary gradient (TPG), and the systemic and pulmonic wedge pressures (PWP) and resistances (PVR and SVR); and calculates the cardiac index and stroke volume [14,28]. Takatsuhi et al. recently reported that the pulmonary arterial capacitance index (PACi), defined as the stroke volume index divided by the pulmonary artery pulse pressure, may serve as a strong prognostic marker in children with IPAH and HPAH [29]. Initial CC should include right and left heart catheterization and AVT. Repeated CCs in children are usually recommended after every 12–24 months for stable cases [28].

AVT is performed for evaluation of the indication and the type of PH specific drugs that can be used for children with IPAH and HPAH and for surgery-related decisions in children with PAH-CHD. Overall, 60–80% of children is non-responsive to AVT [14]. Inhaled nitric oxide (iNO) is used for performing AVT. A combination of iNO (20–80 ppm) plus high oxygen (FiO₂ 0.8–1.0) has been proposed to shorten the study time. Inhaled iloprost may be used as an alternative agent for AVT in children [30]. AVT can induce hemodynamic deterioration during CC, resulting in critical complications, such as rhythm disturbances, PAH crisis, respiratory distress, and even death. To prevent these complications, CC must be conducted at PH centers by experienced physicians [31,32].

In IPAH and HPAH patients, the AVT response is considered positive if there is a 20% fall in both PAP and PVR/SVR ratio without a decrease in cardiac output. In children with significant shunts (Qp/Qs > 1.5), AVT is considered positive if there is a 20% fall in both PVRi and PVR/SVR ratio. Final values of PVRi < 6 WU and PVR/SVR < 0.3 are considered suitable for surgery in PAH-CHD patients [33].

Barst [33] and Sitbon [34] have each suggested potential strategy to classify patients as AVT responders and nonresponders, but consensus has not been achieved [31,32,35]. The consensus statement of 6th. WSPH recommended the Sitbon criteria for a positive AVT response in children with IPAH and HPAH, but most of the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) group recommended the modified Barst criteria due to the lack scientific evidence supporting the use of the Sitbon criteria in children [6,30].

High-resolution chest computed tomography (CCT) along with an angiography is not recommended in case of confirmed etiology because of high radiation exposure. However, it is recommended in children with suspected parenchymal lung disease and in patients who are being evaluated for lung transplantation [36].

Cardiac magnetic resonance imaging (CMR) is an important noninvasive diagnostic test recommended for children with PH for evaluation and follow-up. CMR should be performed at a tertiary center without general anesthesia by experienced medical staff and suitable equipment with special modes of imaging to measure the mass, volume, and function of the heart and lung [37,38]. Pulmonary artery measurements seem to be reliable in CMR because they are independent of body weight and height. Swift et al. recently reported the prognostic value and general use of CMR parameters in PH patients [38].

Serological tests are helpful to assess disease severity, progression, and therapy response [39]. Recent studies showed the usefulness of brain natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NT-proBNP) in children, which are used extensively in adults [40]. Studies have also shown that NTproBNP correlated strongly with survival and disease severity [41] and uric acid levels correlated with the prognosis of pediatric PAH [42]. Serial examination using these serological tests is important during the follow-up of the PH patients to evaluate the outcomes [6].

Circulating endothelial cells (CECs), microRNA, and serum/ plasma cardiac troponin are recommended as useful biomarkers to estimate the risk of surgery or to evaluate disease progression and therapeutic response in children with PAH [39]. Serum/plasma cardiac troponin has been proposed as a biomarker for assessment of PH severity and RV pressure [30]. Serum amyloid A-4 was found to be four-fold higher in children with poor outcomes, and interleukin 6. a proinflammatory cytokine, was associated with adverse events in pediatric PAH. Many biomarkers were found to be related to PAH outcomes [43-46], but none of these biomarkers of disease severity are being used for routine clinical examination [14].

Plasma nitrite/nitrate (NO_{χ}) levels reflect the level of NO synthesis and act as alternative substrate reservoirs for NO synthesis. Zhang et al. reported that circulating NO_{χ} levels in PAH patients were only one-third of the levels found in the control group and that the patients with lower NO_{χ} levels had higher mortality rates. Therefore, NO_{χ} might be a valuable clinical biomarker for disease severity [47].

The genetic background of pediatric PAH patients is different from that of adult PAH patients because of accompanying syndromes, genetic disorders, and growth abnormalities. The mutations found in pediatric PAH patients also differs from those in adult PAH patients [48]. Whether mutation carriers have a different phenotype or clinical course remains to be elucidated [49]. Genetic mutations which are prevalent in PAH mainly include mutations in BMPR2, ACVRL1, ABCC 8, CAV1, TBX4, ENG, EIF2AK4, and KCNK3. Elucidation of these mutations could be beneficial for PH children with unknown etiologies [30].

Further evaluation of various genes such as NOTCH3, SMAD9, GDF2, AQP1, SMAD8, SOX17, and ATP13A3 genes may also be done in children with PAH [30]. Most prevalent mutation is bone morphogenetic protein receptor2 (BMPR2) mutation. Approximately 80% of familial and 20% of IPAH patients carry a heterozygous (BMPR2) mutation. Lower levels of BMPR2 signaling and expression have also been reported in patients with PAH-CHD, PAH-CTD, drug-induced PAH, and interstitial lung disease [48,49]. Patients with BMPR2 mutations, exhibit more severe disease symptoms at a young age and are nonresponsive to AVT, they require more aggressive therapy and have a high risk of mortality. BMPR2 mutation is a strong high-risk criterion even in the absence of other criteria [50-52]. Asymptomatic mutation carriers and family members of the patients should be followed-up using echocardiograms and must be provided with genetic counseling. Genetic testing should be routinely performed in all pediatric PH patients.

4. Disease severity, treatment algorithms, and prognosis

4.1. Risk factors

Risk factors should be considered during the commencement of therapy. The list of PH pediatric risk determinants (severity variables) was updated according to the recent guidelines, as shown in Figure 1 [6,8,30]. Risk variables for children are almost the same as those for adults. The World Health Organization (WHO) functional class (FC) is one of the main determinants used for children to test how the child feels and function. Although it is a subjective assessment, it is a strong predictor of transplant-free survival and can be used as a treatment goal. Clinical evidence of right heart failure, the severity of symptoms, and growth failure must be evaluated for risk stratification. The six-minute walking test (6MWT) can be used to evaluate the exercise capacity. It is technically easy and inexpensive however unfortunately it is not suitable for children under 6 years of age who are not capable to perform it [53]. 6MWT also helps in the assessment of arrhythmia risk, the severity of disease, and therapy response [6,53,54]. Cardiopulmonary exercise test (CPET) is more complicated to be performed for small children. Accelerometry using a wrist or hip device might be employed to monitor the clinical and physical performance in children with PAH [6]. Diagnostic tests are also evaluated for risk stratification. (Figure 1)

4.2. Treatment algorithms

Due to the complex etiology and insufficient comparative data on the efficacy of various therapies with respect to the cause, the decision of suitable therapies in children remains difficult. Taking different etiologies into consideration, many different treatment algorithms for pediatric PAH patients have been proposed, most of which were modified adult recommendations or were based on pediatric experiences [5,54]. In adult and pediatric treatment algorithms, the main goal is to achieve vasodilation of the pulmonary arteries through one of the three pathways and relieve the clinical symptoms. However, most treatment protocols recommend off-label medications for children. Therapeutic algorithms in children differ on the basis of the etiology and functional class. PPHN, BPD, and CDH cases have different protocols from IPAH, HPAH, and CHD-PAH cases. CTD-PAH is extremely rare and usually asymptomatic in children. Regardless of the etiology, all pediatric PAH patients benefit from PAH-targeted drugs. Two algorithms that are applicable to IPAH/HPAH and PAH-CHD are shown in Figure 1, and Table 3 [6,8,9,14,30].

In CHD-PAH children with PVRi > 8WUm2, the defect must not be closed. The children with PVRi 6–8 WUm2 represent high-risk patients of the intermediate zone. The treat and repair or the treat and close approach might be considered for this group and, selectively, in a small subgroup of children with PVRi > 8WUm2. PAH-targeted therapy as single or combination therapy is started preoperatively and is continued for



Figure 1. Diagnosis and treatment algorithms in pediatric IPAH / HPAH.

AVT: Acute vascular reactivity test; BNP: brain natriuretic peptide; CI cardiac index; ERA: endothelin receptor antagonist; HF: heart failure; mPAP: mean pulmonary artery pressure; mSAP: mean systemic arterial pressure; HPAH:Hereditary pulmonary arterial hypertension; IPAH:Idiopathic pulmonary arterial hypertension; PACI: pulmonary arterial capacitance index; PDE-5i: Phosphodiesterase 5 inhibitor; TTE: Transthoracic echocardiography. Modified with permission from [30]

a long time postoperatively. Fenestrated patch closure or pulmonary artery banding might be considered for the patients of this group. The inoperable (Eisenmenger) group can improve their FC via the use of PAH-targeted drugs as combination therapy. In children with a single ventricle, the operability criteria for Fontan surgery includes mean TPG \leq 6 mmHg, PVR < 3WU, and mPAP < 15 mmHg. When Fontan circulation fails, PAHtargeted therapies with endothelin receptor antagonist (ERA) phosphodiesterase inhibitor (PDE5i,) and inhaled iloprost

Table 3. Algorithm for the management of patients with PAH-CHD (shunt lesions) ^a.

-	-		
Hemodynamics	AVT	PAH Therapy	Surgery
Qp/Qs > 1.5	Optional	_	Shunt Closure ^b
O_2 sat> 95			
PVRI < 6 WU m2	Optional	supportive therapy. (monotherapy ?)	Shunt Closure ^b
PVR/SVR<0.3			
PVRI 6–8 WU m2	Necessary	Combination therapy	Shunt closure ^c
PVR/SVR 0.3-0.5	AVT (+)		
	AVT (-)	Combination therapy	Repeat CC
PVRI > 8 WU m2	Necessary	Combination therapy	High risk surgery Patch fenestration ^d
PVR/SVR>0.5	AVT (+)		
	AVT (-)	Combination therapy	Inoperable

^aThis algorithm does not cover the patients with complex cardiac malformations and left heart lesions, they must be evaluated on an individual basis. ^bConsider age, failure to thrive, size and type of the lesion, and associated syndromes.

^cGrey zone predicts uncertainty. Upfront dual oral combination therapy (PDE-5i + ERA± PGi)

^dPAH targeted therapy preoperatively and postoperatively.(Dual or triple combination).

Abbr: AVT, acute vaso-reactivity test; CC, cardiac catheterization; CHD, congenital heart disease, PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; Qp, pulmonary flow; Qs, systemic flow; SVR, systemic vascular resistance; WU, wood unit.

should be considered to improve their FC and hemodynamic parameters [14,30].

The data showing the safety and efficacy of targeted therapies in complex congenital heart disease are not sufficient. PHtargeted therapies can be beneficial against BPD but there are limited trails that assess the effect of these therapies on BPD. PAH-targeted drugs, like sildenafil, iloprost, epoprostenol, and ERA are beneficial against PPHN and in selective critically ill newborns depending on their clinical conditions.

In HPAH and IPAH children with severe disease, initiation of intravenous (IV) epoprostenol or treprostinil along with a combination of PAH-specific drugs should be considered. In the mild disease group, oral monotherapy with an ERA, such as bosentan or ambrisentan; a PDE-5 inhibitor, such as sildenafil; or tadalafil can be used. If the condition of the child deteriorates, sequential, or upfront combination therapy should be considered.

4.3. Prognosis

The prognosis of pediatric PAH is heterogeneous. It's prognosis varies even within a group. Children with left to right shunts suffer from transient PAH, which completely resolves after shunt closure, leading to an excellent prognosis; however, in a small group of patients, PAH persists even after surgical repair and the prognosis is very poor. PAH cases with small coincidental defects resemble IPAH cases. Concomitant genetic disorders and chromosomal syndromes (Trisomy 21, 18, 22, etc.) and growth retardations worsen the prognosis. Complex CHDs and congenital left heart lesions present with poor prognoses and need multidisciplinary approaches. In the last two decades, PAH-targeted therapies have improved prognosis significantly in pediatric PAH patients.

5. Therapeutic measures in PAH

5.1. General measures

Children with mild to moderate PAH are advised to self-limit their activities to avoid breathlessness. Children in the severe disease category are advised to perform the light exercise and play sports, but competitive sports are not allowed. All routine vaccinations are recommended. In addition, pneumococcus and influenza vaccines and RSV immune prophylaxis (for the infants less than 2 years of age) are useful to avoid lung infections. Antibiotic prophylaxis for infective endocarditis is recommended for cyanotic patients and postoperative patients.

Oxygen should be provided to hypoxemic PH patients (oxygen saturation $^{\circ}$ 92% or PaO₂ $^{\circ}$ 60 mm Hg) and the patients with parenchymal or interstitial lung disease and intrapulmonary shunts. Children with PH may fly on commercial airplanes but traveling at high altitudes (>2500 ft) without oxygen support is not advisable [5,6,8,39].

Administration of diuretics, digoxin, and anticoagulants should be considered for treatment on an individual basis. In patients with PAH, diuretics decrease right ventricular overload and alleviate the symptoms. Careful dose adjustment is crucial because PH patients with high PVR are often preload-dependent in order to maintain their cardiac output. Depending on studies on adult patients, aldosterone antagonist spironolactone improves RV and LV diastolic functions [8]. The effects of chronic use of anticoagulants in children with PAH are still unclear. Owing to the hemorrhagic complications immense caution is required when using anticoagulation therapy in progressive IPAH and HPAH patients [14]. Anticoagulation is indicated during the treatment of children with chronic thromboembolic pulmonary hypertension (CTEPH), in children with a hypercoagulable state, and in children with a central venous line. Indications and the drug preference for anticoagulation in children should be critically reviewed. To date, there have been no randomized clinical trials (RCTs) about the use of anticoagulants in pediatric PAH patients.

The use of digitalis for PAH treatment is controversial. Digoxin can be used in patients with right heart failure and atrial arrhythmias to improve right ventricular function and metabolism. The decision on its use must be made on an individual basis. Before starting PH-targeted medical therapy, the underlying causal factors should be eliminated.

5.2. Targeted pharmacological therapy

The PAH-targeted therapies employed for children are mostly based on the data obtained from the studies on adults and pediatric expert opinions. There are few evidence-based therapies that target the underlying pathological process. Determining the risk level and the AVT response is crucial before starting the therapy.

There are three main classes of targeted PAH therapies, which affect three main pathways: the prostacyclin pathway, the NO pathway, and the endothelin pathway. The drugs mainly used against pediatric PAH are listed in Table 4.

5.2.1. Calcium channel blockers (CCBs)

CCBs decrease calcium influx into the smooth muscle cells (SMCs) of the arterial wall and myocardial cells, by inhibiting L-type voltage-dependent calcium channels. CCBs have hypotensive and negative inotropic effects, which make their use contraindicated in right heart failure patients, WHO FC IV patients, infants, and AVT non-responders. Surgical repair instead of CCB therapy is considered for AVT responders with a left to right shunts. CCBs are beneficial in repaired CHD and IPAH children. Generally, CCBs have limited utility in the long-term medical management of pediatric PH. Commonly used CCBs are nifedipine, diltiazem, and amlodipine (Table 4) [56,57].

5.2.2. Prostacyclin (PGI 2) pathway

Prostacyclin has powerful vasodilator, antithrombotic, antiinflammatory, and anti-proliferative properties. It activates protein kinase A through a cyclic adenosine monophosphate pathway, which leads to smooth muscle relaxation. It has previously been demonstrated that adults with IPAH and children with CHD exhibit an imbalance in the biosynthesis of thromboxane A₂ and prostacyclin and decreased prostacyclin synthase expression in their lungs [58,59].

The therapeutic efficacy of prostaglandins has been demonstrated by a randomized controlled prospective study in 1996. This study reported improvement in survival, pulmonary hemodynamics, and QOL in IPAH patients, and the use of epoprostenol for the treatment of severe PAH was approved [60].

5.2.2.1. Epoprostenol. Epoprostenol (sodium salt) is a synthetic form of the prostacyclin and the first PH-targeted drug approved by the FDA. Major pharmacological effects of epoprostenol include vasodilation of the pulmonary and systemic arteries and inhibition of platelet aggregation. Epoprostenol is accepted as the 'gold standard' for the treatment of severe PAH [9,60,61]. However, there are some limitaowing to its pharmacological characteristics. tions Epoprostenol is unstable in solution form and has a very short half-life (3-5 min). Hence, it must be delivered intravenously through a catheter via a portable infusion pump. However, this approach results in other complications, such as thrombosis and line occlusion, local and systemic infections, catheter breakage, and pump malfunction. These complications can lead to severe clinical endpoints. Therefore, more stable prostacyclin analogues with longer half-lives are being explored.

5.2.2.2. Treprostinil sodium. Treprostinil sodium is a PGI_2 analog with a neutral pH and a longer half-life. It is stable at room temperature (up to 72 h) and has the same pharmacological properties as epoprostenol. These characteristics allow

this drug to be administered intravenously, subcutaneously, orally, or by inhalation. In cases that showed worsening of clinical symptoms or intolerance to epoprostenol, the exchange between epoprostenol and treprostinil might be a viable approach [62]. When higher doses are required, intravenous treprostinil is better tolerated. However, risks of infusion delivery system still persist. Recently, to alleviate the risks of an external prostacyclin delivery system, an internalized IV pump and catheter infusion system was developed to treat patients with stable PAH [63,64]. Subcutaneous administration of treprostinil has been approved in Europe and the US for PAH patients with FC II-IV symptoms [10]. Usually, patients prefer oral therapy alternatives because of infusion site pain and risk of infection and thrombosis. Murali et al. conducted a 24-week open-label study at six centers and concluded that lower-risk patients that are treated with parenteral treprostinil could be switched to a more convenient oral form of the drug [62].

Epoprostenol or treprostinil are recommended for WHO FC IV pediatric patients and/or those with rapidly progressive PAH. For severe and progressive disease prostanoid therapy should be started without delay in the form of monotherapy or dual/triple combination therapy [65]. Instead of epoprostenol, IV treprostinil or IV iloprost can be considered. Subcutaneous administration of treprostinil may be preferred in children with severe PH, but pain on the infusion site could pose a problem. A dual or triple combination therapy with prostacyclin analogs and oral PAH-targeted drugs (bosentan, sildenafil, etc.) might result in a better long-term survival in children with severe PAH [61].(Table.5)

5.2.2.3. *Iloprost.* Iloprost is a carbocyclic analog of PGI_2 , and its inhalation and intravenous forms are available. Its inhalation (Inh.) form was approved by the FDA and European authorities in 2004 and 2009, respectively. Data from non-randomized trials stated that intravenous administration of iloprost improved the hemodynamics and FC in PAH patients, and its efficacy is similar to that of epoprostenol. Inh. iloprost rapidly enters the systemic circulation with peak concentration as that obtained just after inhalation stops; the serum half-life is short (20–25 min), so its doses are administered six to nine times a day [59,61].

5.2.2.4. Selexipag. Selexipag is an orally active prodrug metabolized to a highly selective prostaglandin I2 receptor agonist. It exhibits a vasodilatory effect on both large and small pulmonary arteries and have a half-life of more than 6 h [10]. In a selexipag related study on adults, improvement in the 6MWT, and reduction in PVR with tolerable side-effects were observed [66]. A recent report on pediatric PAH patients stated that the patients were able to receive the target dose of selexipag with tolerable side effects and showed improved hemodynamics [67]. However, more studies are needed to elucidate its long-term effects in children.

5.2.3. Endothelin-1 (ET-1) pathway

Endothelins (ETs) are a group of vasoconstrictor isopeptides consisting of ET-1, ET-2, and ET-3. ET-1 is a potent vasoactive peptide mainly produced by the vascular endothelial cells

CCB* Nifedip	Drug Name	Dosage	Adverse Effects	Comments
	oine (oral)	Starting dose: 0.1–0.2 mg/kg x3/d	Bradycardia, Decreased cardiac output, Edema, Rash, Gum hyperplasia, Constipation	Duration of benefit may be limited even with initial favorable response, repeat assessment for response. Contraindicated in age < 1 year
Diltiaze	em (Oral)	Starting dose: 0.5 mg/kg x3/d Dose range 3–5 mg/ kɑ/d	Same above	Same above
Amlodi	ipine (oral)	Starting dose: 0.1–0.3 mg/kg/d dose range 2.5–7.5 mg/d	Same above	Same above
NO pathway PDE5 Sildene inhibitors (IV)	afil (oral)	Age< 1 y: 0.5–1 mg/kg x3/d weight ⁺ 20 kg: 10 mg x3/d weight>20 kg: 20 mgx3/d (IV) 0.4 mg bolus/3 h	Headache, Nasal congestion, Flushing, Agitation, Hypotension, Vision and hearing loss, Priapism.	iv sildenafil may be used in PPHN (COR II b, LOE C) postop CHD** Avoid higher dosing. Approved in Europe and Canada, FDA: warning for use in children. Avoid nitrates.
Tadalai	fil**(oral)	Starting dose: 0.5–1 mg/kg/d max. dose 40 mg/d. Evaluated only in children >3 years	Same above	Safety and efficacy data in children are limited
Endothelin pathway Bosent ERAs anta	tan* dual ETA, ETB agonist (oral)	Weight, < 10 kg: 2 mg/kg x 2/d, 10–20 kg: 31.25 mg x2/d, 20–40 kg: 62.5 mg x2/d, >40 kg: 125 mg x2/d	Hepatotoxicity, anemia, edema, teratogenicity, male infertility, may decrease sildenafil level	Also effective in Eisenmenger
Ambris anta	sentan**Selective ETA igonist (oral)	Dose range: 5–10 mg/d use in pediatric patients< 5 y unstudied	Same above	Safety and efficacy data in children are limited, avoid use in neonates or infants
Macite	intan dual ETA, ETB igonist (oral)	Dose range: 3 mg/d or 10 mg/d in adults (SERAPHIN trial)	Hepatotoxicity, peripheral edema	Approved for adult PAH
Prostacyclin pathway Epopro	ostenol*(iv)	Starting dose: 1–2 ng/kg/min. infusion in pediatric pt. 50–80 ng/kg/min. Max.dose 150 ng/kg/min.	Flushing, jaw, foot, bone, pain, headaches, diarrhea, hypotension, catheter complication	Standard therapy for severe PH
Trepro: and (inh.)	stinil*(Remodulin) (iv sc) .)	Starting dose: 2 ng/kg/min in pediatric patients stable dose 50–80 ng/kg/min. (inh)18mcg x4/day	Flushing, muscle pain, headaches, diarrhea, site pain in sc use	For iv and sc use
llopros inha Selexip (oral	st** (intermittent nlation) oag IPreceptor agonist) ()	6–9 inhalation per day each lasting 10–15 min. Start with 2.5 μg, up to 5 μg Initial dose 200 mcg x2/d increase by 200 mcg/d at weekly intervals max. dose 1600 mcg x2/d	Flushing, jaw pain, headaches, reactive airway symptoms Flushing, headache, diarrhea, vomiting, myalgia, arthralgia	For inhalation "* nebulizer required, patient activation and controlled inhalation, limited by age Approved for adult PAH
Soluble guanylate Riocigu cyclase (sGC) stimulator	uat (oral)	Initial dose 0.5 mg x3/d if blood pressure >95 mm Hg increase the dose with two weeks intervals to max dose (2.5 mg x3/d)	Headache, palpitations, peripheral edema, dizziness, dyspepsia, nausea, diarrhea, vomiting, gastritis, constipation.	Approved for adult PAH

(VECs) and vascular smooth muscle cells (VSMCs) [68]. Its activity is mediated by two receptor subtypes (ETA and ETB). ETA receptors are located on VSMCs, and they mediate vaso-constriction. ETB receptors are located on VECs, and they mediate vasodilation via two mechanisms-firstly via release of NO and prostacyclin (PGI₂), and secondly as clearance receptors for circulating ET-1 [14]. ETA/ETB selectivity is not important for the treatment preference because both the nonselective (bosentan) and selective (ambrisentan) endothe-lin receptor antagonists exhibit a similar degree of positive effects in PAH treatment.

5.2.3.1. Bosentan. Bosentan, a nonselective ET receptor antagonist, decreases PAP and PVR and improves exercise capacity in adults with PAH [69]. Bosentan is the first approved medication in its class and is recommended for the treatment of WHO FC III–IV patients over 12 years of age. It was approved by the FDA in 2017 for pediatric use. It was also approved by the EMA for children over 1 year of age. Many pediatric randomized, placebo-controlled trials have demonstrated the efficacy and safety of this drug in children [70–73].

Elevated levels of aminotransferases were reported as an adverse effect in 2.7% of children less than 12 years of age versus 7.8% of adult patients. For PAH patients with CHD, ERAs have been proven efficient in both monotherapy and combination therapy. Bosentan is also recommended for Eisenmenger syndrome [74] A recent systematic review and meta-analysis by Kuang et al. showed that bosentan was a safe and efficient medicine for PAH-CHD in both child and adult patients, as well as for Eisenmenger syndrome and closed shunt patients [75].

5.2.3.2. Macitentan. Macitentan is a dual endothelin receptor antagonist with a long half-life, administered once-daily. It is approved for adults in the US and Europe [76]. It is well tolerated and significantly reduces the risk of PAH-related hospitalization, and the first PAH-related event [76,77]. There are ongoing trials regarding the effects of macitentan in patients with Eisenmenger syndrome and portopulmonary PH and its effect on right ventricle remodeling in PAH patients [77–79]. However, a recent study on macitentan in ES pediatric patients reported that macitentan did not show superiority over placebo [78].

5.2.3.3. Ambrisentan. Ambrisentan is a selective ETA receptor antagonist. It blocks the vasoconstrictor effects of ETA receptors and maintains the vasodilator/clearance function of the ETB receptors. The FDA has approved ambrisentan for adult patients. Adults treated with ambrisentan showed significant improvement both in terms of clinical performance and hemodynamics, and the incidence of elevated hepatic transferase level was 2.8% which was lower than the patients using bosentan. A study on pediatric patients suggested that ambrisentan in children is safe and effective in the alleviation of PAH symptoms and improvement of hemodynamics [80].

5.2.4. Nitric oxide (NO) pathway (phosphodiesterase-5 inhibitors and soluble guanylate cyclase stimulators)

NO modulates several physiological processes in the body; it dilates blood vessels, and inhibits leucocyte adhesion, platelet aggregation, thrombus formation, and vascular proliferation [81]. Its effects on SMCs, myocytes, and platelets are modulated through soluble guanylate cyclase (sGC) and cyclic guanosine monophosphate (cGMP). Phosphodiesterases (PDEs) are a group of enzymes that inactivate cAMP and cGMP [10]. PDE-5 is excessively released in lung and vascular smooth muscles and has a high activity. Its function is upregulated in PAH patients, resulting in endothelial dysfunction. The inhibition of PDE-5 affects the remodeling and vasodilatory functions of endogenous NO. PDE-5 inhibitors are frequently used both for outpatient therapy and for critically ill patients. Due to their high efficacy and well-tolerated side effect profiles, they are extensively used in pediatric PAH patients.

5.2.4.1. Sildenafil. Sildenafil has been approved for adult WHO FCII–IV PAH patients [82]. STARTS-1 and STARTS-2 studies (randomized, double-blind, placebo-controlled) examined the efficacy of oral sildenafil in pediatric patients [83,84]. The FDA and EMA reviewed the results of these two trials. EMA approved sildenafil for pediatric use with a warning to avoid high doses. The FDA has still not recommended sildenafil in children with PAH but stated that 'there may be situations in which the risk-benefit profile may be acceptable.' (http://3w. fda.gov/drugs/drugsafety/ucm 317123.htm) High doses of oral sildenafil (defined in the STARTS-1 and –2 trials), either as monotherapy or as an add-on drug, have a high risk of mortality in children. Sildenafil and tadalafil are PDE-5 inhibitors.

Oral sildenafil is useful in iNO weaning in critically ill patients such as post-operative patients with PAH, PH-related lung disease, and PPHN. In children with mild or moderate symptoms, the initiation of oral PAH-targeted therapy with PDE-5i and/or ERA as a monotherapy or combination therapy is recommended. Intravenous sildenafil may be considered for PPHN patients, who are treated with or without iNO [30]. It may also be considered in children with PAH-CHD during the postoperative period or for PAH crisis.

5.2.4.2. Tadalafil. Tadalafil is highly selective for PDE-5 isoenzyme, and its half-life is longer than that of sildenafil. The PHIRST-1 and -2 studies showed that tadalafil improved exercise capacity and functional class and reduced the incidence of clinical deterioration in PAH patients; furthermore, longterm treatment with tadalafil led to more beneficial effects [85,86]. Tadalafil is approved for adults, but tadalafil-related trials for pediatric patients are limited. Takatsuki et al. conducted a study on 29 children with PAH who switched from sildenafil to tadalafil for convenient dosing. They stated that the change was well tolerated, and the patients showed significant improvements in terms of hemodynamics [87]. Data from Japanese post-marketing surveillance (PMS) regarding the safety and efficacy of tadalafil in pediatric patients with PAH showed that the frequencies of adverse drug reactions (ADRs) and severe ADRs (SADRs) are significantly lower in pediatric patients than in adults, and that survival rates in

pediatric patients during first and second years were 98.3% and 93.7%, respectively. They concluded that up to an acceptable level tadalafil could be safely used in pediatric patients [88]. Although the use of tadalafil for pediatric patients is not approved yet, there have been a few studies that reported the safety, tolerability, and efficacy of tadalafil in pediatric PAH patients [87–89].

5.2.4.3. *Riociguat.* Riociguat, an oral sGC stimulator, directly increases cGMP level in a non-NO dependent way. It also increases the sensitivity of sGC to NO. Riociguat has shown beneficial effects on 6MWT and exercise capacity, delayed clinical endpoint, and reduction in PVR [90]. Riociguat was approved by the FDA for the treatment of adult PAH, and it is the only drug that is approved for patients with PH associated with chronic thromboembolism. Patients with CHD-PAH were examined in PATENT-1-2 studies for the efficacy of Riociguat; they exhibited good drug tolerability and improvement in functional class, 6MWT, PVR, and NT-proBNP levels [91]. The PATENT-CHILD study, a phase three safety and tolerability trial of riociguat, is underway [14]. Recently a case report described the improvement in a child with severe IPAH, after switching from sildenafil to riociguat [92].

6. Combination therapy

The main principle of combination therapy is to simultaneously target three pathways. A multicenteric pediatric survey showed that treatment using combination therapy during the 2000–2010 study period was independently and strongly associated with improved patient survival [9]. Initial combination therapy with two or three drugs in WHO FC II-IV PAH patients, and sequential therapy for non-responders of initial therapy have been recommended by recent guidelines [30]. Initial upfront dual oral therapy is recommended instead of sequential therapy when the patient is at intermediate risk group. If upfront or add-on combination therapy is not successful, the patients could be switched to another drug that targets the same pathway. A switching strategy may not always be possible for pediatric PAH patients because the drugs that are approved for use in pediatric cases are limited. For dual oral therapy, PDE-5 inhibitors plus ERAs could be used. This therapy might be combined with inhalation, intravenous, or subcutaneous prostacyclin agonists, depending on the risk group and clinical progress.

7. Novel therapeutic targets and drugs

There has been extensive research on the development of novel therapeutic drugs and targets and on currently used agents in terms of route of administration and pharmacokinetics. Current pharmacotherapies demonstrate improved hemodynamics, QOL, and survival in PAH patients, but they have limitations, such as short drug half-lives, drug instability, poor organ specificity, and adverse effects. Segura-Ibarra V, et al., in their review, highlighted the advantages of nanoparticles (NPs) for the efficacious treatment of PAH [93]. NPs offer advantages in improving short-term pharmacokinetics of the drugs and increased localization of therapy to diseased tissues, which, in turn, could decrease the adverse effects.

Current PAH treatments target the vasodilation of pulmonary arteries rather than pulmonary vascular remodeling and inflammation. This is mainly because the pathophysiological mechanisms underlying the remodeling of the vessels and perivascular inflammation are not identified yet. However, pulmonary vascular remodeling is the main underlying cause for the rise in PAP and PVR [1]. Experimental and clinical researches are needed to identify the underlying mechanisms of this severe disease and find the therapeutic means to reverse the pulmonary circulation to normal. A recent study reported that prostanoid EP4 receptor (EP4) - protein kinase A(PKA)-nuclear peroxisome proliferator-activated receptor (PPARy) plays an important role in the inhibition of PASMC proliferation and migration. The authors propose EP4-PKA-PPAR as a novel pathway and EP4 as a potential therapeutic target for PAH [94].

Inflammasomes are regulators of inflammation, and they promote the release of proinflammatory cytokines (IL-1B and IL-18) [95]. These cytokines are elevated in PH patients, and IL-6 and the C-reactive protein were also reported to be elevated in children with PAH-CHD [96]. Scott et al., in a recent review, summarized the role of inflammasomes in the pathobiology of PH and concluded that the inflammasome, a key component of the innate immune system, is emerging as a novel target in the treatment of PH owing to its promising potential in preclinical studies [95]. More studies are needed to evaluate the precise function of inflammasome-related cytokines (IL-6, IL-18, IL-1B, and LTB4) and inflammasome components (NLRP3, ASC, and Caspase-1) in PH patients.

7.1. Tyrosine kinase inhibitors, rho kinase inhibitors

The therapeutic efficacy of tyrosine kinase inhibitors, namely, imatinib, nilotinib, and sorafenib, is under investigation for PAH patients. Severe adverse events and cardiotoxicity are important concerns with respect to the safety of these drugs and limit their use in the treatment of PAH.

Rho kinase inhibitors are a new class of therapeutic agents. Rho kinase is an effector of guanosine triphosphate that causes smooth muscle contraction. Fasudil is a specific inhibitor available in intravenous and inhaler forms. A recent study reported that inhalational form decreased systolic PAP and PVR of the patients [97].

7.2. Vasoactive intestinal peptide (VIP)

Vasoactive intestinal peptide (VIP) has been considered a potent new therapeutic target in PAH patients owing to its properties to induce pulmonary arterial smooth muscle cell (PASMC) relaxation, neutralization of vasoconstrictors (ET-1), inhibition of cell proliferation, and anti-inflammatory effects. However, studies employing VIP have not revealed improvement in the patients [98].

7.3. Endothelial progenitor cells (EPCs)

Endothelial progenitor cells (EPCs) can proliferate and migrate in response to angiogenic growth factors and differentiate into mature cells in situ to form a blood vessel. In PAH patients, a deficiency of these progenitor cells might contribute to endothelial dysfunction, and the replacement of these cells could help in, repair and regeneration of the blood vessels. The results of a study on the safety and efficacy of EPC infusion in pediatric IPAH patients showed improvements on exercise capacity and pulmonary hemodynamics [99]. Safety studies and animal trials are still ongoing [100].

8. Surgical and interventional therapies

8.1. Atrial septostomy and the Potts shunt

Atrial septostomy and the Potts shunt are palliative procedures performed to treat syncope and intractable heart failure in patients who are refractory to chronic PAH-targeted therapy [6]. Atrial septostomy with or without device implantation alleviates disease symptoms and QOL in pediatric PAH patients and may serve as a bridge to lung transplantation, which could increase the chance of survival of the patients. Some risks are associated with atrial septostomy including worsening of hypoxemia and right ventricular failure, increase in left atrial pressure and promotion of pulmonary edema, and size reduction or spontaneous closure of the defect. To overcome these risks, fenestrated devices (atrial flow regulators) can be used to keep the atrial septum open [101], or a Potts shunt may be considered as an alternative option. Unlike atrial septostomy, the Potts shunt unloads the pulmonary vascular bed and right ventricle, providing a higher amount of oxygen saturated blood to coronary arteries and central nervous system. The Potts shunt is a surgical or interventional procedure by which the left pulmonary artery and the descending aorta are connected [102]. Surgical or interventional therapies could be valuable alternatives for lung transplantation or a palliation to lengthen the LTx-free survival in selected cases [6]. Although there are promising long-term results, these techniques require further studies and experiences. Surgical and interventional procedures for PH patients must be performed in advanced PH centers.

8.2. Lung transplantation

Lung transplantation should be considered for high-risk patients who do not respond to advanced treatment with PAH-targeted therapy. Overall survival following lung transplantation is similar in pediatric and adult patients, and recent registry data indicates a median survival rate of 4.9 years [103]. Heart-lung transplantation is recommended for PAH-CHD patients, and double lung transplantation is recommended for patients with IPAH.

9. Expert opinion

All the currently available therapeutic agents mainly restore the dysfunction of the pulmonary vascular tone. In addition to their vasodilatory effect, these therapeutic agents exhibit antiproliferative and immune-modulatory effects. However, none of them targets the main cause of the disease; therefore, PAH is still a non-curable fatal disease. This fact encourages trials that focus on pathobiology, novel therapeutic targets and strategies, and biological markers that could be used for risk stratification. Currently, the available data on pediatric PAH diagnosis and therapy are limited because of the lack of randomized controlled clinical studies and epidemiological surveys. The current data and recommendations are mainly derived from guidelines for adults and confirmed by pediatric expert opinions. Moreover, some pediatric PH specialists inevitably use off-label drugs in children with PH.

The progress of the disease in children shows similarities and differences with that in adults. Children display several features that are similar to those in adults. However, the unique nature of pediatric PAH should not be underestimated. For example, neonates and infants present with completely different disease course because of developmental abnormalities. Pulmonary hypertension in neonates might be triggered by prenatal, natal, or neonatal injuries, or factors that affect pulmonary circulation. The etiology, triggering factors, and treatment strategy of PPHN are completely different from those of other patient groups. It is a transient form of PH. However PAH-targeted drugs such as oral and IV sildenafil, IV prostacyclin, inhaled iloprost, or epoprostenol are effective in their treatment. These drugs increased the survival rate in preterm and term babies with PPHN and BPD. Term babies also benefited from ERAs.

Genetic and syndromic anomalies might result in different etiologies and prognoses in pediatric patients. Without treatment, the mortality rate is higher in children than in adults, but targeted PAH therapies achieve better outcomes in children. The course of the disease in children is not always predictable, and the behavior of the disease is usually unique for each child. Among patients with PAH-CHD who have leftto-right shunts, patients in whom PAH would be resolved after shunt closure can not be predicted. Patients with PAH who have small coincidental defects resemble patients with IPAH. Positive acute vasoreactivity response is higher in children than in adults, but children with left to right shunts and Eisenmenger syndrome do not benefit from CCB treatment. In addition, long-term therapy with CCBs is limited in children. However, response to PAH-targeted therapy is much better in children than in adults. This might be due to the ongoing remodeling of the pulmonary vascular structure in children and the prevailing effect of vasoconstriction. Although the etiologies of pediatric and adult PH have several differences the underlying physio-pathological mechanisms are similar. This is the main reason why pediatric and adult patients both benefit from PAH-targeted drugs.

Although the existing palliative therapies are useful for improving QOL and survival rates in children with PAH, studies on the safety and efficacy of the drugs and upfront combination therapy in WHO FC II–III patients must continue. Upfront combination therapies are usually recommended as a standard approach, but the use of combination therapies in children should be considered on an individual basis. The efficacies of PAH-targeted drugs and treatment strategies for PAH in adults have not been adequately studied for pediatric patients because of the low incidence of the disease in children. Multi-center, randomized controlled clinical trials and phases 2 and 3 studies on treatment algorithms and new drugs such as riociguat, selexipag, treprostinil, and macitentan are needed. Investigations on novel drugs targeting the same pathways are important to identify novel alternative therapeutic agents; however, a search for novel therapeutic pathways is also needed. Investigations are also needed to further explain the pathophysiology of PH. In addition, the mechanisms underlying the vasoconstriction and remodeling of the pulmonary vasculature should be elucidated. Genetic mutations, especially in BMPR2, which is accepted as a key regulator of pulmonary vascular homeostasis, should be studied to determine the full extent of their role in PAH pathogenesis. This area is promising for the identification of novel therapeutic targets for PAH. Genetic testing and counseling of patients with PAH must be performed in PAH centers by genetic experts.

During the last decade, a lot of information has been gathered from patient registries, clinical studies, and surveys on children and adults to provide guidelines for diagnosis and treatment strategies of children with PAH. During the last 5 years pediatric PH specialists convened to develop comprehensive and detailed consensus guidelines for pediatric PH. They published the guidelines on the diagnosis and treatment of pediatric PH in 2016 and an updated version in 2019. Certainly, health-care providers treating patients with PAH will benefit from these recommendations. Moreover, guidelines are important to disperse the refined knowledge among relevant physicians and, in turn, obtain comparative data from registries and studies. However, gaps remain in the knowledge regarding the evaluation and treatment of PAH in children, such as reliable and easy determinants of severity, approved drug doses, treatment strategies, goals, and endpoints of clinical trials, place, and timing of bridge procedures, and LTx, which must be elucidated through further study.

The recent definition of PAH has brought forth a new controversy and has introduced a topic of research on the diagnosis and treatment strategy for patients with mPAP between 20 and 25 mmHg. Over- diagnosis and over-treatment are the main concerns regarding this new definition. Children with borderline PAH should be followed up in PH centers owing to their risk for developing PAH. Further studies on related morbidities and outcomes are needed.

Although PAH has no cure yet, recent advances in drug therapies have improved the QOL and survival rates of patients. Moreover, the novel therapeutic strategy for PAH with an early combination of at least two targeted drugs inhibits the progress of disease; thereby decreasing the severity. However, more studies are needed to improve existing knowledge on the pathophysiology of this rare disease. The increasing research and growing number of scientific reports regarding pediatric PAH warrant that future recommendations on pediatric PAH could become evidence-based instead of experience-based, and that off-label drugs would become labeled.

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Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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