EXPERT OPINION

Treating pulmonary hypertension in pediatrics

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Introduction: Pulmonary hypertension is a hemodynamic condition occurring rarely in pediatrics. Nevertheless, it is associated with significant morbidity and mortality. When characterized by progressive pulmonary vascular structural changes, the disease is called pulmonary arterial hypertension (PAH). It results in increased pulmonary vascular resistance and eventual right ventricular failure. In the vast majority of cases, pediatric PAH is idiopathic or associated with congenital heart disease, and, contrary to adult PAH, is rarely associated with connective tissue, portal hypertension, HIV infection or thromboembolic disease.

Areas covered: This article reviews the current drug therapies available for the management of pediatric PAH. These treatments target the recognized pathophysiological pathways of PAH with endothelin-1 receptor antagonists, prostacyclin analogs and PDE type 5 inhibitors. New treatments and explored pathways are briefly discussed.

Expert opinion: Although there is still no cure for PAH, quality of life and survival have been improved significantly with specific drug therapies. Nevertheless, management of pediatric PAH remains challenging, and depends mainly on results from adult clinical trials and pediatric experts. Further research on PAH-specific treatments in the pediatric population and data from international registries are needed to identify optimal therapeutic strategies and treatment goals in the pediatric population.

Keywords: pediatrics, pulmonary hypertension, registries, strategy, treatment goals, treatments

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1. Introduction

Pulmonary hypertension (PH) is a hemodynamic condition defined by an increased pulmonary artery mean pressure (mPAP) above or equal to 25 mmHg [1]. This can be associated with multiple clinical conditions forming different etiological groups with specific and diverse pathological and pathobiological characteristics [2]. Pulmonary arterial hypertension (PAH) is a rare disease that is characterized by PH, normal pulmonary artery wedge pressure (PAWP ≤ 15 mmHg) and elevated pulmonary vascular resistance (PVR) that is due to substantial and characteristic remodeling of small-caliber pulmonary arteries with proliferation of endothelial and smooth muscle cells and medial hypertrophy [3]. The consequences of these changes in the pulmonary vasculature are progressive right ventricular (RV) overload, hypertrophy, dilatation and eventually RV failure and death. Even if the pathobiology and pathophysiology of PAH are not completely elucidated, the major pathways involved in the development and progression of the disease are well identified [4] and include the overexpression of endothelin (ET), a potent endothelium-derived vasoconstrictor peptide with strong mitogenic properties [5]. Decreased activities of vasodilator and antiproliferative vasoactive mediators, such as prostacyclin and nitric oxide (NO), have also been demonstrated [2,6]. As a consequence, the PAH-specific drug therapies developed during the last 20 years target these pathways, whereas several new ones are currently being explored (**Figure 1**) [7]. The

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Article highlights.

- Pediatric pulmonary arterial hypertension (PAH) is a rare disease that leads to right heart failure.
- The last decade has seen the emergence of several new PAH-specific drug therapies and new potential therapeutic pathways.
- Current therapeutic strategy and treatment goals depend mainly on results from adult clinical trials and pediatric experts.
- Children with PAH are currently and most of the time treated with off-label PAH-specific drug therapies.
- Large registries have been developed to offer better knowledge and define more precisely pediatric PAH.

This box summarizes key points contained in the article.

emergence of PAH-specific drug therapies dramatically changed the prognosis of this progressively life-threatening group of conditions [8-11]. So, even if there is still no cure for PAH except lung or heart–lung transplantation, the major progresses in its management allow it to be considered as a chronic disease, spanning throughout childhood and adulthood. The aims of the present review are to give an overview of the current available medical therapy and to highlight the main challenges for treating PH in pediatrics, both now and in the future.

2. Characteristics of pediatric PH

2.1 Classification and nomenclature

Despite sharing many characteristics with adults, pediatric PAH is associated with proper multifactorial and heterogeneous underlying diseases [12]. Among the differing features should be included etiology, the underlying condition, the prevalence of congenital heart diseases (CHDs), the impact of the disease on a growing child, its progression rate and prognosis [13-15]. According to the Pediatric Task Force of the Pulmonary Vascular Research Institute, pediatric pulmonary hypertensive vascular diseases are indeed related to 10 main pathophysiological classes (**Table 1**), which could justify a proper subdivision [16]. Nevertheless, the international classification of PH that was updated after the 2013 World Symposium on PH in Nice [2] aimed to create and maintain five common groups for both adults and children (**Table 2**). Group 1 (PAH) includes new established genetic disorder causing PAH (SMAD 9, Caveolin, Potassium channel KCNK3, and T-box 4 [small patella syndrome]). Persistent pulmonary hypertension of the newborn (PPHN) presents particular anatomical aspects, physiological origins and time course resulting in a specific management [17]. As a consequence, it has been placed in a separate Group 1 subcategory. Congenital and acquired left heart inflow and outflow tract obstruction have been added to Group 2 while developmental lung diseases and associated abnormal lung vascular growth have been added in Group 3. Therefore, several specific aspects related to pediatric PH were added, as this unification should help physician and dedicated health-care providers to insure continuity in the transition from childhood to adulthood follow-up.

2.2 Epidemiology

Large registries, including the TOPP registry [12] (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension), the Nationwide Netherlands PH service registry [18] and the combined adult and pediatric US REVEAL registry [11] (Registry to Evaluate Early and Long-Term PAH Disease Management), have been developed to offer better knowledge and define more precisely pediatric PH. PAH etiologies in the pediatric population remain heterogeneous, and their distribution is very different from adults [19], with a predominance of idiopathic (IPAH) or associated with CHD (APAH-CHD). In contrast with adults, PAH associated with connective tissue disease, portopulmonary hypertension (PPH), HIV infection or chronic thromboembolic PH (CTEPH) are infrequent in children [11,12]. In the Netherlands registry [18], the yearly incidence rates for PH were 63.7 cases per million children. The annual incidence rates of IPAH and APAH-CHD were 0.7 and 2.2 cases per million, respectively. The prevalence of APAH-CHD was 15.6 cases per million. The incidences of PPHN and transient PH associated with CHD were 30.1 and 21.9 cases per million children, respectively.

2.3 Diagnostic strategy

Due to the multifactorial and heterogeneous underlying causes of PAH in children, the diagnostic strategy needs to be precise, rigorous and comprehensive (**Figure 2**). One should also remember that the correction of the potential underlying abnormality or disease that cause or could contribute to the development of PAH has to be considered before the patient is initiated with PAH-specific drug therapy. At this point, one should also remember that results from the TOPP registry revealed that pediatric patients with suspected PH rarely benefit of a full diagnostic workup [12]. This could be partially explained by occasional suboptimal collaboration of pediatric patients or estimated prohibitive risk associated with certain procedures [20]. Whatever the reasons, this is a major concern as complete diagnostic workup should be assured before pediatric patients are managed with the most appropriate treatment. Because PH is a hemodynamic condition, hemodynamic evaluation by right heart catheterization is mandatory for diagnosis. The importance of acute vasoreactivity testing (AVT) during hemodynamic workup must also be outlined as it allows not only detecting patients with IPAH eligible for calcium-channel blocker (CCB) treatment but also evaluating operability of patients with CHD, considering generally that acute responders with PAH associated with congenital shunt lesions are considered candidates for surgical repair. It may also give invaluable information about the prognosis of the disease [21]. This convincingly demonstrates the paramount importance of addressing children with a

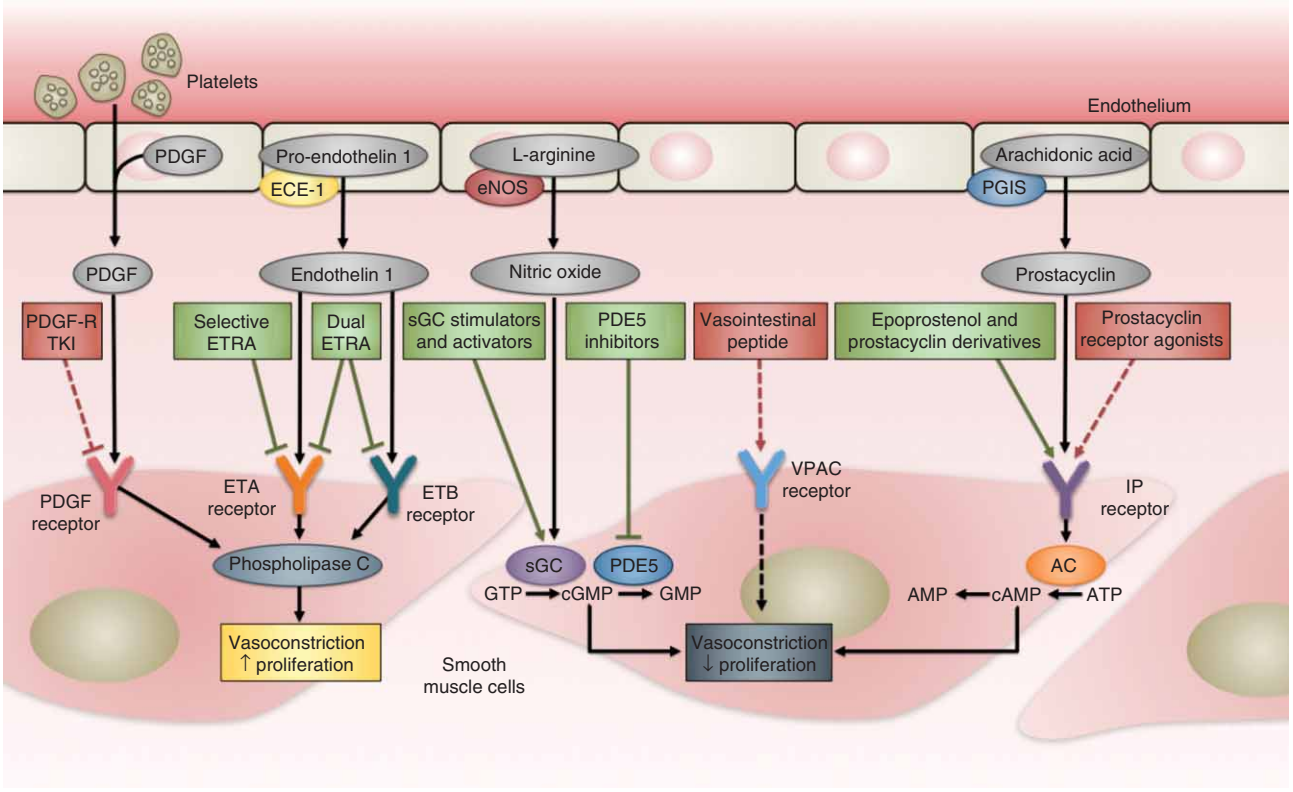

Figure 1. Current and emerging targets and therapies for PAH. Pulmonary artery smooth muscle cell therapeutic targets and corresponding licensed (green boxes) and investigational (red boxes) treatment approaches for PAH. Arrows represent receptor stimulation, whereas terminated lines show receptor blockade.

Adapted with permission from [7].

AC: Adenylate cyclase; ECE-1: Endothelin converting enzyme 1; eNOS: Endothelial nitric oxide synthase; ERA: Endothelin receptor antagonists; ETA: Endothelin receptor type A; ETB: Endothelin receptor type B; IP: Prostaglandin I2; PAH: Pulmonary arterial hypertension; PDE5: PDE type 5; PDGF: Platelet derived growth factor; PDGF-R TKI: PDGF receptor tyrosine kinase inhibitors; PGIS: Prostaglandin I synthase; sGC: Soluble guanylate cyclase; VPAC: Vasointestinal peptide receptor.

Table 1. Broad schema of 10 basic categories of pediatric pulmonary hypertensive vascular disease (Panama classification).

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

10 broad categories of pediatric pulmonary hypertensive vascular disease listed in order of frequency.

Reproduced with the permission from [16].

PAH: Pulmonary arterial hypertension.

suspicion of PAH in expert centers for diagnostic workup and management.

2.4 Prognosis

The historical National Institutes of Health registry reported, without treatment, a median survival rate of 10 months after IPAH diagnosis [22]. Before the availability of PAH-specific drug therapies, a single-center cohort study reported an estimated median survival of 4 years in children with IPAH [23]. In the modern therapeutic era, the survival rate of pediatric patients has continued to improve with a similar life expectancy to that seen in adults. Children in the REVEAL registry demonstrated 1-, 3- and 5-year estimated survival rates from diagnostic of 96 ± 4%, 84 ± 5% and 74 ± 6%, respectively [11]. Retrospective reports from the UK and Netherlands have shown variable but also significantly improved survival rates for pediatric PAH. Although overall survival has improved in recent years, some patients, such as those with PAH and repaired CHD, may present unfavorable outcome [15,18,24].

Table 2. Classification of PH (Nice classification).

Pulmonary arterial hypertension
Idiopathic PAH (IPAH)
Heritable PAH (HPAH)
BMPR2
ALK-1, ENG, **SMAD9, CA1, KCNK3**
Unknown
Drug and toxin induced
Associated with
Connective tissue disease
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatose
1″. Persistent pulmonary hypertension of the newborn
PH due to left heart disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
PH due to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorder
Chronic exposure to high altitude
Developmental lung diseases
Chronic thromboembolic PH
PH with unclear multifactorial mechanisms
Hematologic disorder: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytose
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorder
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

Udapted classification of pulmonary hypertension. The bold cases signal the modification as compared with de Dana Point classification.
Reproduced with permission from [2].
BMPR2: Bone morphogenetic protein receptor type II; CAV1: Caveolin 1; ENG: Endoglin; KCNK3: Potassium channel K3; PAH: Pulmonary arterial hypertension; PH: Pulmonary hypertension.

2.5 Prognostic factors

Currently known prognostic factors in pediatric PAH patients are reported in the **Table 3** and present similarities with adult PAH population [25,26]. Interestingly, elevated World Health Organization functional class (WHO-FC) is represented although not designed for pediatric population, whereas 6-minute walk distance (6MWD) has not been shown to predict survival, possibly due to a ceiling effect of this procedure [15,27] and because 6MWD is understandably an unreliable measurement for children under 5 – 6 years old. Failure to thrive is specific to pediatrics and is associated with a worse prognosis [27].

2.6 General management

Although there is no clear recommendation concerning the general management of pediatric PAH [25], it should be emphasized that allowance of normal activities of childhood without the need to self-limit is an important goal of care. As it is the case for adult PAH [26], physical activities should be encouraged, avoiding strenuous exertion that leads to severe breathlessness. Although rehabilitation program is currently recommended for adult, there is currently no data for the pediatric population. Because infection may be a cause of PAH worsening, pediatric patients should closely follow vaccination schedule. While there are no controlled trials, experts recommend vaccinating against influenza and pneumococcal pneumonia [26].

3. Supportive care

In the modern therapeutic era, physicians and caregivers should always remember that the control of central venous pressure, the treatment of cardiac arrhythmia and the correction of hypoxemia should be achieved first in PAH. Inexpensive and so-called conventional therapies are available for this endeavor. For example, the use of diuretics is essential in the management of patients with PH related to left heart disease and is necessary in the management of RV failure. There, it should be used carefully as preload is an important determinant of cardiac output. Oxygen therapy may be considered in case of severe resting or exercising hypoxemia. The use of digitalis is controversial, but may improve RV metabolism and function [28]. The use of anticoagulation remains a problem in pediatrics, as risk of bleeding should be balanced with a potential beneficial effect that has not been proven in this population. Experts suggest to anticoagulate pediatric patient with over RV failure and dilatation. The use of anticoagulation in patients with Eisenmenger syndrome is controversial, as it has not been shown to improve long-term survival and may increase the risk of hemoptysis and cerebral hemorrhages [29]. More generally, the balance between thromboembolic and anticoagulation risks and benefits should be assessed on individual basis but could still be in favor of anticoagulation when dealing with increased thrombosis risk factors induced by central venous catheters and very low cardiac output.

4. General considerations about PAH-specific drug therapy

During the last 20 years, the discovery of new pathophysiological and pathobiological pathways and the development of new specific therapeutic options have drastically changed the management and fate of pulmonary hypertensive vascular diseases [9,10]. However, because the pediatric population present specificities, it still remains difficult to systematically transfer conclusions from adult data to children. Therapeutic

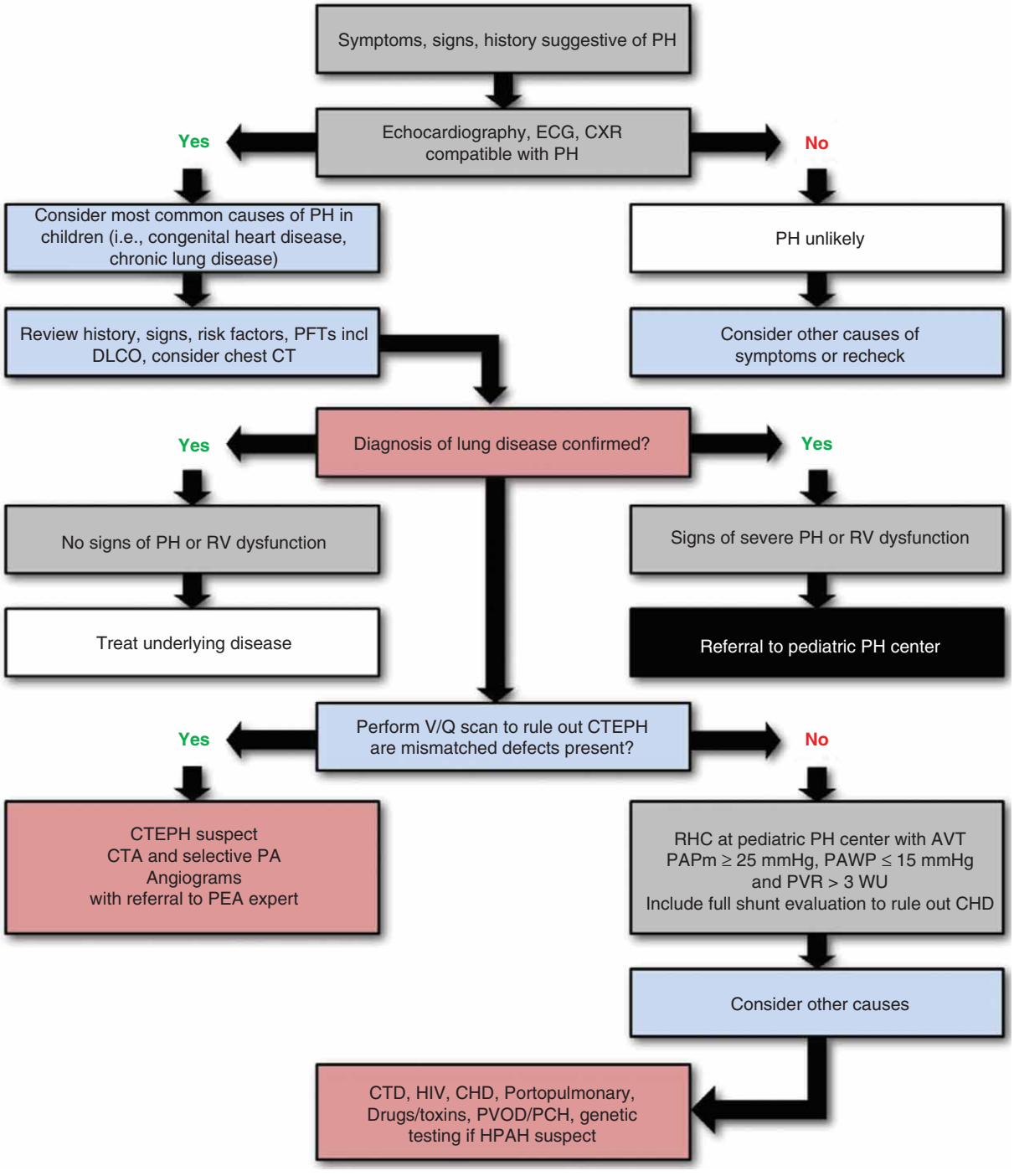

Figure 2. Pulmonary hypertension diagnostic strategy in pediatrics. If a reliable test cannot be obtained in a young child and there is a high index of suspicion for underlying lung disease, the patient may require further lung imaging. Children 7 years of age and older can usually perform reliably to assess exercise tolerance and capacity in conjunction with diagnostic work-up.
Adapted with permission from [25].
AVT: Acute vasodilator testing; CHD: Congenital heart disease; CTA: Computed tomography angiography; CTD: Connective tissue disease; CTEPH: Chronic thromboembolic pulmonary hypertension; CXR: Chest radiography; DLCO: Diffusing capacity of the lung for carbon monoxide; ECG: Electrocardiogram; HPAH: Heritable pulmonary arterial hypertension; PA: Pulmonary artery; PAH: Pulmonary arterial hypertension; PAPm: Pulmonary artery mean pressure; PAWP: Pulmonary artery wedge pressure; PCH: Pulmonary capillary hemangiomatosis; PEA: Pulmonary endarterectomy; PFT: Pulmonary function test; PH: Pulmonary hypertension; PVOD: Pulmonary veno-occlusive disease; PVR: Pulmonary vascular resistance; RHC: Right heart catheterization; RV: Right ventricle; V/Q: Ventilation/perfusion; WU: Wood units.

Table 3. Determinants of risk in pediatric PAH.

Lower risk	Determinants of risk	Higher risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I,II	WHO-FC	III, IV
Minimally elevated	BNP/NT-proBNP	Significantly elevated, rising level
	Echocardiography	Severe RV enlargement/dysfunction
		Pericardial effusion
Systemic CI > 3.0 l/min/m^2	Hemodynamics	Systemic CI < 2.5 l/min/m^2
mPAP/mSAP < 0.75		mPAP/mSAP > 0.75
Acute vasoreactivity		RAP > 10 mmHg
		PVRI > 20 WU m^2

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BNP: Brain natriuretic peptide; CI: Cardiac index; mPAP: Pulmonary artery mean pressure; mSAP: Systemic artery mean pressure; NT-proBNP: N Terminal pro-BNP; PAH: Pulmonary arterial hypertension; PVRI: Pulmonary vascular resistance index; RAP: Right atrial pressure; RV: Right ventricle; WHO-FC: World Health Organization functional class; WU: Wood units.

strategies for adult PAH have still been poorly studied in children, and appropriate end points for goal-oriented therapy in children are only emerging [30]. As a consequence, the US FDA and the European Medicines Agency (EMA) did not yet approve most of the available PAH-specific treatments except sildenafil for the EMA. Hence, children with PAH are currently and most of the time treated with off-label PAH-specific drug therapies, whereas 10 molecules are approved for adults [31]. These therapies are presented hereafter and reported with their potential pediatric use in **Table 4**.

5. PAH-specific drug therapies

5.1 Calcium-channel blockers

CCBs cause relaxation of vascular smooth muscle and are indicated for children with a positive AVT [32]. This is the case in 7 – 40% of children with chronic PAH [33,34]. Acute responders with PAH associated with congenital shunt lesions are considered candidates for surgical repair [35]. In responders to AVT in repaired CHD or IPAH, CCBs may be considered. The most commonly used vasoreactivity criteria include the Barst criteria (decrease in mPAP of ≥ 20%, unchanged or increased cardiac index, and decreased or unchanged pulmonary to systemic vascular resistance ratio) [36], Rich criteria (decrease in mPAP and PVR of ≥ 20%) [37] and Sitbon criteria (decrease in mPAP of ≥ 10 mmHg reaching an mPAP value of < 40 mmHg and an increased or unchanged cardiac output) [38]. However, specific studies for pediatric patients, such as the Sitbon study, are not available. So the current definitions of responder can formerly not be applied for assessing feasibility of surgical repair. Nifedipine, diltiazem and amlodipine are the preferred CCBs for PAH therapy and should be used with caution in patients with severe ventricular dysfunction, elevated right atrial pressure and low cardiac output as it may further decrease ventricular contractility. These treatments should be avoided in infants in the first year of life because it may have a potentially deleterious negative inotropic effect. Improved survival under CCB therapy has been reported in pediatric patients demonstrating a sustained response [32], but careful monitoring is essential as patients may deteriorate with CCB monotherapy.

5.2 Endothelin receptor antagonists

The pathophysiological role of ET, a potent vasoactive peptide produced primarily in the vascular endothelial and smooth muscle cells, is well established in PAH [5]. Two types of receptors mediate ET: type A (ETA) and type B. The FDA has approved oral, selective and nonselective, endothelin receptor antagonists (ETRA) therapies in adult PAH after demonstrating exercise capacity, hemodynamics and survival improvements [39,40]. Oral ETRAs are generally well tolerated, and classical adverse events include abdominal pain, nausea, flushing, headache, leg edema, hypotension and nasal congestion [41,42]. Important clinical side effects of ETRA therapy include liver enzyme elevation, anemia, seminiferous tubular atrophy and impaired fertility [42,43]. Due to the risk of teratogenicity, pregnancy should be avoided during ETRA therapy. It is noteworthy that oral contraception can also be ineffective with ETRA therapy, so use of another reliable method of contraception is recommended in childbearing-age teenager. Three ETRAs are currently available for adult PAH treatment in the USA and Europe: bosentan, ambrisentan and macitentan. A fourth ETRA, Sitaxsentan, was withdrawn from the market in 2010 following the recognition of a pattern of idiosyncratic liver injury [44]. Although the use of ETRAs in pediatric patients with IPAH or APAH has demonstrated clinical benefit, ETRAs have not been approved for use in pediatric populations in the USA. However, bosentan, an oral dual ETRA, has been approved but

Table 4. Specific drug therapies approved for adult PAH treatment and their use in pediatrics.

Drug class	Drug name	Way	Use	FDA	EMA	Initial dose	Target dose	Maximum adult dose
CCB	Nifedipine	PO	Y	N	N	0.2 – 0.3 mg/kg t.i.d.	2 – 5 mg/kg/day	120 – 240 mg/day
	Amlodipine	PO	Y	N	N	2.5 – 5 mg/day	5 – 10 mg	20 mg/day
	Diltiazem	PO	Y	N	N	1.5 – 2 mg/kg/day	3 – 5 mg/kg/day	240 – 720 mg/day
ETRA	Bosentan	PO	Y	N	**Y***	2 mg/kg‡ 10 – 20 kg: 16 mg b.i.d.§ 20 – 40 kg: 32 mg b.i.d.§ > 40 kg: 62.5 mg b.i.d.§	2 mg/kg b.i.d.‡ 10 – 20 kg: 32 mg b.i.d.§ 20 – 40 kg: 62.5 mg b.i.d.§ > 40 kg: 125 mg b.i.d.§	125 mg b.i.d.
	Ambrisentan	PO	Y	N	N	< 20 kg: 2.5 mg/day > 20 kg: 5 mg/day	5 mg/day 10 mg/day	10 mg/day
	Macitentan	PO	N	N	N	N/A	N/A	N/A
PDE5i	Sildenafil	PO	Y	N	**Y**	< 8 kg: 0.5 mg/kg t.i.d.	1 mg/kg t.i.d., max 30 mg/day	40 mg t.i.d.
				N	**Y**	8 – 20 kg: 10 mg t.i.d.	10 mg t.i.d.	
				N	**Y**	> 20 kg: 20 mg t.i.d.	20 mg t.i.d.	
		IV	Y	N	**Y**	0.4 mg bolus in 3 h	1.6 mg/kg/day (continuous)	10 mg t.i.d. (bolus)
	Tadalafil	PO	Y	N	N	1 mg/kg/day, max 40 mg/day	1 mg/kg/day, max 40 mg/day	1 mg/kg/day, max 40 mg/day
sGCS	Riociguat	PO	N	N	N	N/A	N/A	2.5 mg t.i.d.
Prostacyclin	Epoprostenol	IV	Y	N	N	1 – 3 ng/kg/min	50 – 80 ng/kg/min	Upon tolerance
	Treprostinil	IV	Y	N	N	1.25 – 2 ng/kg/min	50 – 80 ng/kg/min	Upon tolerance
		SC	Y	N	N	1.25 – 2 ng/kg/min	50 – 80 ng/kg/min	Upon tolerance
		Inh.	Y	N	N	3 breaths (18 mcg) 4×/day	9 breaths (54 mcg) 4×/day	9 breaths (54 mcg) 4×/day
	Iloprost	IV	Y	N	N	N/A	N/A	> 2 ng/kg/min, upon tolerance
		Inh.	Y	N	N	2.5 mcg per inhalation 6 – 9×/day	5 mcg per inhalation 6 – 9×/day	5 mcg per inhalation 6 – 9×/day
	Beraprost	PO	N	N	N	N/A	N/A	N/A

*Approved for use but not labeled.

‡With the pediatric formulation (available in Europe only).

§With the adult formulation.

b.i.d.: Two times a day; CCB: Calcium-channel blocker; EMA: EMA approved; ETRA: Endothelin receptor antagonist; FDA: FDA approved; Inh: Inhaled; IV: Intravenous; N: No; N/A: Not available; PAH: Pulmonary arterial hypertension; PO: Per os; SC: Subcutaneous; sGCS: Soluble guanylate cyclase stimulator; t.i.d.: Three times a day; Use: Currently used for treating pediatric-PAH; Way: Way of administration; Y: Yes.

not labeled by EMA in 2009 for use in a pediatric formulation.

5.2.1 *Bosentan*

Several pediatric studies have explored and demonstrated clinical utility of bosentan therapy, including improvement of exercise capacity, WHO-FC and long-term outcomes in children with IPAH and PAH-CHD [15,27,41,45-47]. It has been approved for treatment of PAH in adults by the FDA in 2001 and by the EMA in 2002. The safety of bosentan therapy in children with PAH has been recently reported [46]. Two retrospective studies of children treated with bosentan also demonstrated sustained clinical and hemodynamic improvement with no significant adverse events with an estimated 2-year survival around 90% [48,49], whereas a third one that included 86 children with IPAH, heritable PAH or APAH had an estimated 4-year survival of 82% and a disease progression of 54% [50]. Bosentan has also demonstrated clinical, hemodynamics and exercise capacity improvement in pediatric and grown-up patients with APAH-CHD characterized by systemic-to-pulmonary shunt [51]. Bosentan also improved these parameters without worsening hypoxemia in patients with adult Eisenmenger syndrome in a 16-week, multicenter, randomized, double-blind, placebo-controlled trial (RCT) [47]. The European-approved formulation of bosentan in pediatric PAH is 2 mg/kg two times daily. Liver enzymes should be monitored monthly. One may also mention that bosentan demonstrated pharmacological interactions with PDE-5 inhibitors (PDE5i, see Chapter 5.3). This could have been an issue when considering multiple PAH-specific combination therapy but the clinical significance of this interaction is uncertain.

5.2.2 *Ambrisentan*

Ambrisentan is an oral selective ETA receptor antagonist. It has been approved for treatment of PAH in adults by the FDA in 2007 and by the EMA in 2008, as it demonstrated improvements in exercise capacity and delayed clinical worsening, with a satisfying safety profile [52,53]. Data reporting experience, clinical outcome or pharmacokinetics with this medication in

pediatrics are scarce and further studies are needed to definitely confirm the clinical efficacy of ambrisentan in this population. Safety of this PAH-specific treatment was further suggested by a recent report where patients reported nonsignificant elevation of liver enzyme levels [54]. In a single-center study, patients with Eisenmenger syndrome treated with ambrisentan increased exercise capacity without long-term hypoxemia or clinical worsening [55]. This therapeutic option is attractive in children with PAH; first, because it demonstrated a risk of liver enzymes' perturbation similar to the placebo group in a large multicenter RCT. Consequently, the FDA withdrew the recommendation to test liver enzymes on a regular basis. Second, ambrisentan utilization appears easier as it presents no drug interaction with PDE5i and then facilitates combination therapy. Third, pharmacological profile obtained from adult and retrospective pediatric clinical data allow a once-daily dosing. Pediatric patients could be initiated at 2.5 or 5 mg once daily depending on patient weight < 20 or > 20 kg with a target dose of 5 mg or 10 mg, respectively, and as tolerated. It is important to report here that a randomized open-label study that aimed evaluating safety, tolerability and efficacy of a high- and low-dose ambrisentan in pediatric patients suspended recently recruitment, as reported on *clinicaltrials.gov* (NCT01332331). Hence, further data are awaited in order to describe more precisely the place of ambrisentan in the treatment of PAH in pediatrics.

5.2.3 *Macitentan*

Macitentan is a novel dual ERA with tissue-targeting properties that is thought to have improved receptor-binding capacity than any other ERA and fewer drug–drug interactions than bosentan. It has been approved for treatment of PAH in adults by the FDA and by the EMA in 2013 after publication of the results of a large multicenter RCT with morbidity and mortality endpoints demonstrating a delay in disease progression in adult PAH [56]. There is currently no data available for the pediatric population. A multicenter RCT (MAESTRO; Macitentan in Eisenmenger Syndrome To Restore Exercise Capacity) is currently recruiting and aims to assess the efficacy, safety and tolerability of macitentan in subjects over 12 years old with Eisenmenger's syndrome. It is planned to perform a study in the pediatric population, as the once-daily formulation is appealing as well as the lack of potential liver side effects.

5.3 PDE-5 inhibitors

PDE5i prevent the breakdown of cGMP, resulting in pulmonary vasodilation. PDE5i also have antiproliferative and proapoptotic properties. Moreover, PDE5i appear to be highly expressed in the hypertrophied human RV, and acute inhibition with oral sildenafil has been shown to improve RV contractility [57]. Adverse effects include headache, flushing, exacerbation of nosebleeds, and rare systemic hypotension or erections. Transient color vision disturbance may occur due to a crossed PDE6i effect. Routine vision and hearing assessments are not recommended but should be considered with long-term PDE5i treatment, especially in premature infants. PDE5i are usually administered orally with a satisfactory tolerance profile and are approved by FDA and EMA for the treatment of PAH in adults.

5.3.1 *Sildenafil*

The FDA and the EMA approved Sildenafil in 2005 for the treatment of adult PAH as it was found to improve exercise ability and delayed time to clinical worsening at a dose of 20 mg three times daily [58]. The potential utility of Sildenafil was rapidly recognized and suggested by preliminary case reports and case series. Further studies provided arguments for the safety and efficacy of this medication in pediatric PAH [59,60]. Then, the results of the awaited worldwide RCT STARTS-1 (Sildenafil in Treatment-Naive Children, aged 1 – 17 years, with pulmonary arterial hypertension) were released [61]. In this study, children with untreated PAH received orally three times daily low-, medium- or high-dose Sildenafil or placebo. The primary outcome was percent change in peak oxygen consumption (VO_{2peak}) in patients able to exercise and failed to reach statistical significance for the merged combined Sildenafil doses. In fact, the low dose appeared ineffective and a *post hoc* analysis excluding this group revealed significant change in VO_{2peak} against placebo. Secondary endpoints, including mPAP, PVR and WHO-FC, were assessed in all enrolled patients and improved dose dependently, improvement getting statistically significant only for medium- and high-dose Sildenafil. In the long-term extension study (STARTS-2) [62], children on therapy remained on the dose of sildenafil received during STARTS-1, but were unblinded. Children receiving placebo were randomized (stratified by weight) to low-, medium- or high dose. At 3 years, an increase in mortality was noted at the higher doses with deaths appearing to be dose-related. Three-year Kaplan–Meier survival rates were of 94, 93 and 88% for the high-, medium- and low dose, respectively. In fact, survival was favorable for all dose groups but hazard ratios for mortality were 3.50 (95% CI 1.29 – 9.51) for high- versus low-dose sildenafil. Review of these data by the FDA and the EMA resulted in disparate recommendations. Sildenafil was approved by the EMA in 2011, with a later warning on avoidance of use of the high dose. In August 2012, the FDA released a strong warning against the chronic use of Sildenafil for pediatric patients with PAH. In response to the FDA position, the Scientific Leadership Council of the Pulmonary Hypertension Association released a consensus statement regarding several limitations of the STARTS-2 trial [63], especially considering i) the absence of untreated control group; ii) that there was an lack of safety and efficacy data for combination therapy; and iii) the overall favorable survival as compared to historical controls. Similar to the conclusions made by the EMA the group recommended continuing with caution the use of oral sildenafil in pediatric patients, with a strong recommendation to avoid high doses.

Recently, FDA has issued a clarification to the earlier warning acknowledging that *"there are situations in which the individual risk/benefit ratio may be acceptable."* One may also note that the current FDA position does not apply to children < 1 year old and to the use of sildenafil in the intensive care setting.

Sildenafil may also be useful in the setting of inhaled NO therapy withdrawal in several clinical situations like postoperative PH [64], PPHN [65] or in single ventricle physiology with high PVR [61]. In children with PH associated with chronic lung disease, sildenafil has been shown to improve hemodynamics in 88% of patients without hypoxemia worsening [60]. Although no definitive dosing guidelines have been established in the USA, conservative sildenafil dosing is based on the current EMA recommendations (**Table 4**).

5.3.2 *Tadalafil*

Tadalafil is a long-acting PDE5i. EMA in 2008 and FDA in 2009 approved this medication for the treatment of adult PAH after it was shown to improve exercise capacity and quality of life while reducing clinical worsening in a large multicentric RCT [66]. Interest in Tadalafil raised for the pediatric patients first because it is administered once daily and may further improve therapeutic observance; secondly and mainly because recent data suggest that Tadalafil treatment may be well tolerated in children, offers a favorable side effect profile and provides clinical improvement [67]. In an open-label retrospective study, 29 patients were successfully transitioned from Sildenafil to Tadalafil and reached statistically improved hemodynamics when compared to Sildenafil [67]. Use in the neonatal and infant population is contraindicated. Caution is advised due to lack of data on the use of Tadalafil in infants, whereas 1 mg/kg/day of Tadalafil seems to be well tolerated in children. Tadalafil can also be prepared in a thermo-stable solution that could further facilitate utilization in pediatrics. The reported side effects are similar to those seen with Sildenafil. A pediatric Tadalafil study is currently recruiting patients.

5.4 Guanylate cyclase stimulator

5.4.1 *Riociguat*

Riociguat, an oral agent with dual mode of action that synergizes with endogenous NO and also directly stimulates soluble guanylate cyclase, is a therapy that explores the NO pathway (**Figure 1**). FDA and EMA approved it in 2013 for the treatment of adult PAH and inoperable CTEPH after demonstrating improved hemodynamics, WHO-FC, and time to clinical worsening in large multicentric RCTs [68,69]. No pediatric studies have been completed.

5.5 Prostacyclin analog

Prostacyclin is a metabolite of arachidonic acid endogenously produced by the vascular endothelium. It is a potent pulmonary and systemic vasodilator with antiplatelet, antithrombotic, antiproliferative and anti-inflammatory activity. Patients with severe PAH present decreased level and activity of prostacyclin metabolites and prostacyclin synthase [70]. After CCBs, prostacyclin therapy was the only available PAH-specific therapy for a decade and the approval of ETRA and PDE5i. It has improved functional status and survival for both adult and pediatric patients.

5.5.1 *Epoprostenol*

Epoprostenol was the first available prostacyclin therapy and was approved by FDA in 1995. Due to rapid pharmacokinetics with a half-life of ~ 3 – 5 min, it requires administration by continuous intravenous infusion, placement of a permanent central venous catheter and delivery by a portable infusion pump. The emergence of the previously discussed oral specific therapy in the last 10 years simplified drastically PAH management but also imposed a shift of indication for Epoprostenol that is currently recommended as first-line treatment only for adult PAH patients with severe symptoms (WHO-FC III or IV) [26]. Although it is still not approved in children, continuous intravenous Epoprostenol therapy is also effective for improving symptoms, hemodynamics and survival in this population [32,34]. Moreover, down transition to oral or inhaled specific PAH therapy was successful in patients who improved largely hemodynamics [71]. Due to the complicated nature of dose titration, Epoprostenol therapy should be initiated in a PH expert center during a dedicated hospitalization. In a monitored hospital setting, intravenous epoprostenol is initiated at 1 – 3 ng/kg/min and the dose is rapidly increased over the first few days, and then steadily increased by 1 – 2 ng/kg/min every 1 – 2 weeks as tolerated. Dose titration can be managed on an outpatient basis, with the goal to maximize efficacy while side effects remain tolerable. It has been reported that children may require higher doses than adults, commonly in the range of 50 – 80 ng/kg/min, with further up-titration on an individual basis, but this remains to be validated as some centers use dose range of 20 – 40 ng/kg/min, similar to those of adults. Side effects of Epoprostenol therapy are dose-dependent and usually occur within minutes or hours of dose titration. Common side effects include flushing, headache, nausea, diarrhea, jaw discomfort, foot pain, rash and thrombocytopenia. Severe adverse events such as bradycardia, systemic hypotension and severe thrombocytopenia may occur, resulting from inappropriate dosage. Hypoxemia due to increased ventilation–perfusion heterogeneity may occur or worsens in patients with PH due to lung disease. Life-threatening pulmonary edema may develop in patients with pulmonary veno-occlusive disease. Sepsis secondary to infection of the central catheter, catheter dislodgement or catheter thrombosis can occur and may worsen PAH. This being said, risks and benefits should be cautiously weighed with the family prior to initiation of Epoprostenol therapy in any child despite the strong evidence supporting this therapeutic option. A room-air thermo-stable Epoprostenol formulation is available since 2010 and may simplify and

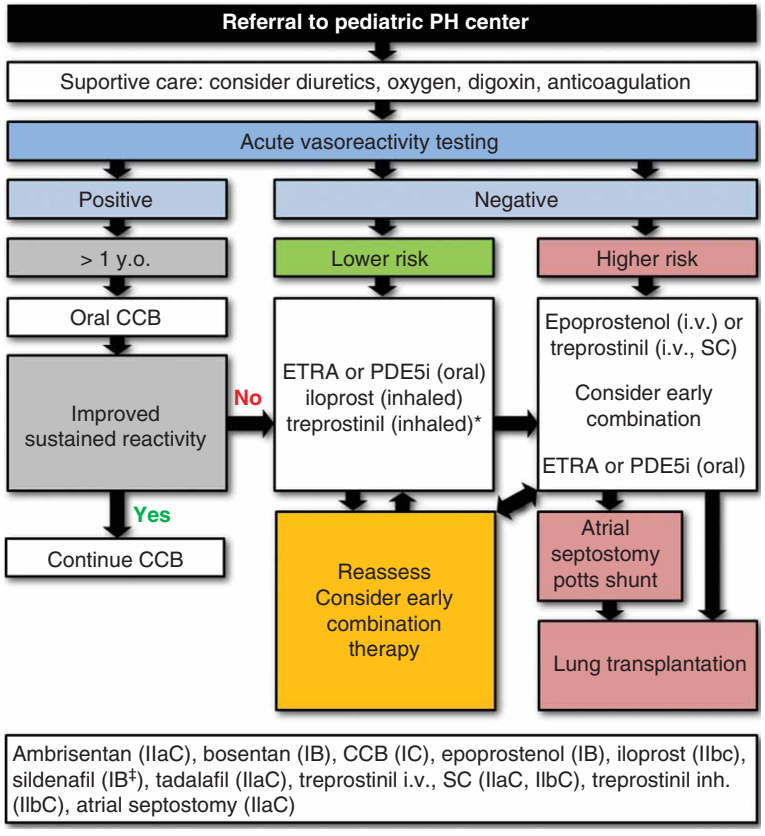

Figure 3. PH therapeutic strategy in pediatrics. World Symposium on Pulmonary Hypertension Consensus (Nice 2013) Pediatric PAH treatment algorithm.

Adapted with permission from [25].

*Use of all agents is considered off-label in children aside from sildenafil in Europe.

‡Dosing recommendations per European-approved dosing for children. See text for discussion of use of sildenafil in children in the United States.

CCB: Calcium-channel blocker; ETRA: Endothelin receptor antagonist; HPAH: Hereditary pulmonary arterial hypertension; Inh: Inhalation; IPAH: Idiopathic pulmonary arterial hypertension; i.v.: Intravenous; PAH: Pulmonary arterial hypertension; PDE5i: PDE 5 inhibitor; PH: Pulmonary hypertension; SC: Subcutaneous; y.o.: Year-old.

secure management by decreasing the frequency of catheter manipulations.

5.5.2 *Treprostinil*

Treprostinil is a prostacyclin analog that was initially approved by the FDA in 2002 for the treatment of adult PAH via continuous subcutaneous infusion. It was then approved for intravenous formulation in 2004 and as inhaled therapy in 2009. Subcutaneous Treprostinil has been shown to improve exercise tolerance, symptoms and hemodynamics in adult PAH patients [72] but discomfort and pain at the infusion site are common and represent an important limiting factor in children. The use of intravenous Treprostinil in children can be considered for patients who have been on a stable dose of intravenous Epoprostenol with clinical improvement [73]. Interestingly, children exhibited fewer side effects despite higher doses. Subcutaneous Treprostinil therapy may also be proposed in children after failure of combined oral treatment or due to severe complications with intravenous Epoprostenol. Typically, continuous infusion through a central venous catheter has been found to expose children to an increased risk of catheter-related bloodstream infections. The recent development of an implantable pump is very promising but it is regrettable that this therapeutic option has been proposed to PAH patients without any prior validation and safety study. Moreover, the size of the currently used pump is a major limitation for its use in younger patients. Intravenous and subcutaneous Treprostinil is generally initiated at 1.25 – 2 ng/kg/min, and the dose is gradually increased based upon clinical status, hemodynamic changes and side-effect profile. A target is typically around 50 – 80 ng/kg/min. Prostacyclin side effects noted with intravenous Treprostinil are similar to those of Epoprostenol. Inhaled Treprostinil has fewer systemic effects and can be started in the outpatient setting in stable patients as add-on therapy. Inhaled Treprostinil is dosed in 6 mcg breaths and the starting dose of inhaled Treprostinil for an adult is three breaths (18 mcg) four times per day. It is generally increased by an

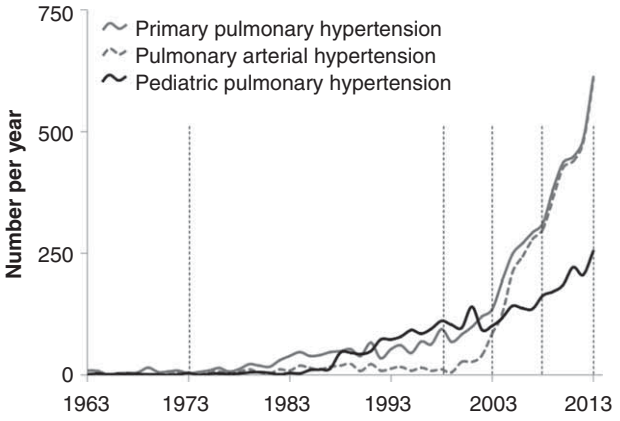

Figure 4. Evolution of the number of publication per year. Evolution of the number of occurrences (publications) listed in PubMed whit the keywords 'treatment' AND 'primary pulmonary hypertension,' 'pulmonary arterial hypertension' or 'pediatric pulmonary hypertension,' respectively. The thin black dashed lines correspond to the five different world symposia on pulmonary hypertension (Geneva 1973, Evian 1998, Venice 2003, Dana Point 2008, Nice 2013). Note that the term 'primary pulmonary hypertension' was officially abandoned after the Evian congress in 1998 and replaced by 'pulmonary arterial hypertension'.

additional three breaths every 1 – 2 weeks as tolerated, to a target maintenance dose of nine breaths per treatment. Children < 20 kg should be monitored for systemic hypotension and may require slower up-titration of one breath every 2 – 4 weeks, with an initial target maintenance dose of five to six breaths (30 – 36 mcg) per treatment. Proper inhalation device and technique are required for effective drug delivery, so patient education and support from relatives and care givers are essential for the management.

5.5.3 *Iloprost*

Iloprost is a prostacyclin analog with an inhaled preparation that has several advantages over intravenous therapy, including lower risk of systemic hypotension and minimizing the effect on ventilation–perfusion mismatch. FDA approved Iloprost in 2004 after demonstration of improvement in hemodynamics and WHO-FC in IPAH and APAH-CHD [74,75]. Due to a short biologic half-life, low risk of toxic metabolites, and ease of delivery, inhaled Iloprost has been considered as an alternative to inhaled NO for postoperative care and vasodilator reactivity testing. Treatment could be initiated with a 2.5 mcg dose of inhaled Iloprost five to nine times daily, then increased to 5 mcg, and maintained at that dose. Lower-airway reactivity and bronchoconstriction may be a problem in some children, together with the risk of poor compliance related to the need for frequent aerosol administrations. Iloprost is also available in intravenous formulation but data are currently limited in the pediatric population.

5.5.4 *Beraprost*

Beraprost is an oral prostacyclin analog that is not currently available in the United States or Europe. In few studies, Beraprost has been shown to improve hemodynamics and exercise capacity in patients with IPAH [76]. An RCT suggested non-sustained clinical benefits over time [77]. Evidence to support the use of Beraprost in children is scarce even if largely used in Asian countries such as Japan.

5.5.5 *Selexipag*

Selexipag is an oral selective prostacyclin receptor agonist and promising new therapy. In a Phase II study, Selexipag was well tolerated with a favorable side effect profile and showed significant reduction in PVR compared with placebo [78]. The results of a large, multicentric, Phase III study should be announced shortly (*clinicaltrials.gov*; NCT01106014).

6. Combination therapy

Combination therapy is the current recommended option for patients worsening with monotherapy (**Figure 3**) and is increasingly used, as seen in pediatric registries whose reports suggest a potential clinical benefit as compared to monotherapy in pediatric PAH [79]. However, the evidence is scarce, depending on data from small prospective cohort [80,81] or retrospective study [82]. Switching to intravenous prostacyclin should also be considered [83]. By simultaneously addressing the PAH multiple pathophysiological pathways, combination therapy may be more efficacious. Concomitant use of targeted PAH therapies has been well tolerated and has been shown to improve exercise capacity, hemodynamics, and time to clinical worsening in adults [84-87]. Whether combination therapy should be used as a first step by up-front initiation of two or more drugs or by addition of a second treatment to a previous therapy considered insufficient is still not known despite recent encouraging reports [88]. More studies are needed to help establish guidelines for combination therapy in children. Until results of such studies are available, either rapid sequential or upfront combination therapy appears most probably the way forward.

7. Treatment strategy and treatment goals

As there is still no cure for PAH, treatment goals must focus on improving survival, quality of life, exercise capacity and hemodynamics. Treatment strategies for pediatric PAH are currently extrapolated from evidence-based adult guidelines where goal-oriented strategy represents a significant progress in PAH management [89]. It has even emerged as the best treatment approach for adult PAH, where medical therapy is increased when goals are not met. Unfortunately, only limited data for treatment strategies in children with PAH exist, due to few randomized controlled clinical trials evaluating the safety and efficacy of specific treatments. In cases of clinical worsening with maximal PAH-specific drug therapy, atrial

septostomy may be considered [90], possibly in combination with a pulmonary-to-systemic shunts (Potts shunt) [91]. Lung or heart–lung transplantation are the last therapeutic options but should be considered early in patients with high risk of deterioration [25].

In fact, goal-oriented strategy is indeed already what is done in most referral centers, upon expert opinion but without any clear evidence. So it is needed to identify the parameters that best correlate with better outcome. A recent report open the way and aimed at identify treatment goals in a pediatric PAH population [92]. In this prospective study, WHO-FC, N Terminal pro-BNP (NT-proBNP) and an echocardiographic parameter (TAPSE, Tricuspid Annular Plan Systolic Excursion) were suggested as PAH-specific treatment-induced improvements in these variables were associated with improved survival. Hence, these results are encouraging and have to be confirmed by larger cohorts and studies.

8. Conclusions

In the last 20 years, the emergence of PAH-specific drug therapies together with the development of strategies for diseases management has allowed improvement of long-term survival of children with PAH. Nevertheless, pediatric PAH remains challenging as treatment use in children is mainly based on experience or expert opinion, whereas most therapies in adults are evidence based on results from RCTs. An increase in international collaboration means that evidence is building up: the number of multicenter trials dedicated to pediatric PAH is increasing. Large-scale international registries will contribute to far improve and refine the goal-oriented strategies for pediatric PH.

9. Expert opinion

The face of PAH has changed considerably in many aspects over the last decades. At this point, it is worth saluting the pioneers of PH's community of experts. When first meeting in Geneva in 1973, and then in Evian in 1998, they laid the cornerstone of a promising and expanding network. This network has managed to educate populations and patients, increase awareness of physicians to PH and to promote the establishment of national reference centers for this group of diseases. This enabled the multiplication of research groups of excellence and generated major scientific publications. For instance, the vivacity of research activity in the field may be outlined by the quantity of scientific reports listed the US National Library of Medicine (PubMed.gov) reported in the **Figure** 4. The results obtained with the keywords 'treatment' and 'pediatric pulmonary hypertension' increased by 75% between 1984 – 1993 and 1994 – 2013 decades. Those including 'treatment' and 'primary pulmonary hypertension' increased by almost 500% in the same period even if 'primary pulmonary hypertension' was officially abandoned and replaced by 'PAH' after 1998. With 10 approved new drugs in 20 years, 9 in the last decade and probably more to come, one should also note that the enthusiasm of the PH community translated into a sustained involvement by pharmaceutical companies. PAH is still a rare and fatal disease but it cannot be considered as orphan illness anymore. This is reflected in its inclusion as a major topic in the 2014 European Respiratory Society international congress.

Of course, pediatricians involved in PH are legitimate to request more evidence about PAH-specific treatment in children. First, there are very few drugs, if any in some countries that are approved for treatment. As we have seen, several studies are indeed currently ongoing to confirm efficacy and safety as well as the adapted pediatric dose for the different medications. Hopefully, these studies will lead to drug approval, as it was the case for EMA after the STARTS studies. One may also acknowledge that the off-label use of PAH-specific treatments in pediatric clinical practice induced data in favor of efficacy and safety of these drugs. Second, the clear definition of treatment goals in pediatric PAH is urgently needed as those currently applied to the adult population may not be adapted to children. In fact, it should be also recognized that most pediatric referral centers wisely apply a goal-oriented strategy for their patients without data confirming its validity. To deepen the knowledge, share expertise, outline emergency and accelerate the processes, the pediatric group benefited from a specific task force at the last World Symposium and was part of the published proceedings related to treatment goals. Since then, we have seen that WHO-FC, TAPSE and NT-proBNP were recognized in a monocentric study and suggested as treatment goals in pediatric PAH. These results are promising and show how close the perspective of pediatric goal-oriented therapy is. Surely, they have to be confirmed in a larger cohort of patients but similar results are expected from ongoing studies or from the large registries we cited earlier.

The pediatric PAH community has recently made a lot of progress to improve the diagnosis and treatment of PAH, but there is probably still a long quest before a cure is found. Until then, the optimization of PAH management by the approval of existing and emerging drugs and the consecutive development of ambitious goal-oriented strategies are probably the key elements in providing the best care for these fragile patients.

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Declaration of interest

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