

ORIGINAL ARTICLE

Diagnostics, monitoring and outpatient care in children with suspected pulmonary hypertension/paediatic pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK

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ABSTRACT

Pulmonary hypertension (PH) is a condition of multiple aetiologies with underestimated prevalence and incidence. Indeed, despite access to modern therapies, pulmonary hypertensive vascular disease (PHVD) remains a progressive, usually life-limiting condition, severely impacting on the patients' well-being. We herein provide practical, expert consensus recommendations on the initial diagnostic work-up, clinical management and follow-up of children and adolescents with PH/PHVD, including a diagnostic algorithm. The major topics and methods that need to be tailored and put into context of the individual patient include PH classification, clinical signs and symptoms, basic diagnostic and advanced imaging measures (ECG, chest X-ray, transthoracic echocardiography, cardiac magnetic resonance, chest CT angiography, cardiac catheterisation, ventilation-perfusion lung scan, abdominal ultrasound), lung function tests, 6 min walk and cardiopulmonary exercise testing, sleep study (polysomnography), laboratory/immunological tests, considerations for elective surgery/general anaesthesia, physical education and exercise, flying on commercial airplanes, vaccinations, care of central intravenous lines and palliative care. Due to the complexity of PH/PHVD, the clinical care has to be multidisciplinary and coordinated by a dedicated specialist paediatric PH centre, not only to decrease mortality but to allow children with PH/PHVD to reach a reasonable quality of life.

INTRODUCTION

Pulmonary hypertension (PH) is a condition of multiple aetiologies, sharing a significant increase in pulmonary artery pressure. For the majority of patients, PH represents a progressive and life-limiting disease with significant impact on quality of life, especially in the advanced stages of disease.

Diagnostic algorithms and implementation of careful disease monitoring and follow-up are desirable to standardise medical care, gain further insight into disease progression, guide therapy, facilitate multicentre trials and, ultimately, achieve best possible

Box 1: Definitions

Pulmonary Hypertension (PH)

mPAP ≥ 25 mmHg in children >3 months of age at sea level

Pulmonary Arterial Hypertension (PAH)

mPAP ≥ 25 mmHg
PCWP < 15 mmHg
PVR index > 3 WU \times m²

Idiopathic PAH (IPAH)

PAH with no underlying disease known to be associated with PAH

Hereditary PAH (HPAH)

PAH with no underlying disease but with positive family history or positive genetic testing

Pulmonary Hypertensive Vascular Disease (PHVD)

For biventricular circulations:

mPAP ≥ 25 mmHg and PVR index > 3 WU \times m²

For circulations with cavopulmonary anastomosis (e.g., Fontan physiology):

mean TPG > 6 mmHg (calculate mPAP minus mLAP or PCWP) or PVR index > 3 WU \times m². Detailed hemodynamic definitions of PH (e.g., precapillary vs. postcapillary PH, value of the diastolic transpulmonary pressure gradient) are presented in Apitz C, Hansmann G, Schranz D. Heart, 2016[1]. mPAP, mean pulmonary artery pressure; mLAP, mean left atrial pressure; PAH, pulmonary artery hypertension; PCWP, pulmonary capillary wedge pressure (syn. PAWP, pulmonary artery wedge pressure); PVRi, pulmonary vascular resistance index; TPG, transpulmonary pressure gradient.

clinical outcomes. Consensus standardisation is particularly important because PH, especially pulmonary arterial hypertension (PAH), is a rare condition and single-centre experience is often limited.^{1 2}

The aim of this article is to provide an overview over the condition and existing classifications. Moreover, we introduce a paediatric diagnostic



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algorithm and practical recommendations for the monitoring and outpatient care of children and adolescents with PH, PAH and/or pulmonary hypertensive vascular disease (PHVD).

METHODS

The recommendations on diagnostics, monitoring and outpatient care in paediatric PH given in [table 1](#) are based on a grading system currently suggested by the European Society of Cardiology (ESC) and the American Heart Association (AHA), and was based on paediatric data only (class of recommendation, level of evidence). The grading and voting process within the writing group is outlined in the executive summary⁶⁹ of this special issue. Computerised searches of the PubMed/MEDLINE bibliographic database from 1990 to June 2015 were conducted. The developer searched using the terms ‘paediatric pulmonary hypertension’, ‘pulmonary hypertension and children’, ‘pulmonary hypertension and children and: diagnosis/diagnostics; follow-up, monitoring, epidemiology, classification, symptoms, functional classification, electrocardiogram, imaging, chest X-ray (CXR), echocardiography, lung function test, six-minute walk test, cardiopulmonary exercise testing, polysomnography, sleep study, computed tomography (CT), cardiac catheterization, magnetic resonance imaging (MRI), ventilation-perfusion scan, abdominal ultrasound, portal hypertension, chronic thromboembolic pulmonary hypertension, laboratory testing, serological markers, biomarkers, genetic testing, (lung) transplantation, palliative care, general anaesthesia, risk, surgery, flying, air travelling, contraception’.

DEFINITION

PH has been defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg at rest, measured by cardiac catheterisation (according to the most recent 5th World Symposium on Pulmonary Hypertension, Nice 2013). The term pulmonary arterial hypertension (ie, group 1 PH) describes a subpopulation of patients with PH, characterised haemodynamically by the presence of pre-capillary PH, including an end-expiratory pulmonary artery wedge pressure < 15 mm Hg and a pulmonary vascular resistance > 3 Wood units.^{3–4} While this definition has been widely accepted for paediatric use,⁵ the Pulmonary Vascular Research Institute (PVRI) expanded it and introduced the term ‘paediatric pulmonary hypertensive vascular disease (PPHVD)’ in 2011 (Panama, 2011). Importantly, the Panama classification distinguishes between PH with and without pulmonary vascular disease (PVD), between single and biventricular circulations, and acknowledges the heterogeneous aetiology in paediatric PH that can even have prenatal (fetal) origins. Although patients with congenital heart disease (CHD) and single-ventricle physiology (without subpulmonary ventricle) often do not meet the criteria as defined above (ie, mPAP < 25 mm Hg, but PVD evident), they may benefit from similar pharmacological strategies and share some clinical features of patients with PH. For patients with Fontan-type haemodynamics (no subpulmonary ventricle), a PVR index > 3 WU \times m² or a transpulmonary gradient of > 6 mm Hg has been suggested as a definition of PPHVD.⁴ The most common type of PH diagnosed in childhood is PAH associated with CHD. Frequently, PAH-CHD presents with a pre-tricuspid or post-tricuspid shunt lesion (eg, left-to-right shunt) with or without evident PVD. Children without PVD benefit from shunt closure.⁷⁰ Children with established PAH and PVD (PPHVD) may not tolerate shunt closure due to the sudden loss of decompression of the RV. The onset and progression of PAH-CHD and consecutive PVD differ in pre-tricuspid versus post-tricuspid lesions since the latter (eg, a large ventricular septal defect (VSD)), may

expose the pulmonary vasculature not only to increased flow but also systemic or near-systemic pressure.

While adults with classical Eisenmenger haemodynamics actually have a better survival than patients with idiopathic pulmonary arterial hypertension (IPAH)/hereditary pulmonary arterial hypertension (HPAH), children with PAH-CHD and those with IPAH have a similar mortality with a 5-year survival reported to be 71% and 75%, respectively.⁶

PH CLASSIFICATION

Nice World Symposium classification (2013) and Panama PVRI classification (2011)

Whereas the first international classification for PH was based on histological findings,⁷ more recent classifications (Evian 1998, Venice 2003 and Dana Point 2008) were refined with a focus on common clinical features, pathophysiology and to delineate differences and similarities of the various entities of the disease.

At the last World Symposium of Pulmonary Hypertension in Nice (2013, [table 2](#)), a new subgroup of ‘multifactorial PH’ was introduced to account for the heterogeneity of paediatric PH and special considerations that apply to children.⁸

The Paediatric Taskforce of the PVRI addressed the need for a more specific paediatric classification, introducing the concept of hypertensive vascular disease (PPHVD), that is, PH with elevated PVR, and focusing on issues and disease entities that are particularly relevant to children.⁴ In 2011, a new Paediatric Panama classification was proposed ([table 3](#)), suggesting 10 categories of PPHVD. The Panama classification takes perinatal maladaptation, insufficient development and pulmonary hypoplasia, as well as genetic findings into account, all of which may play a role in the development of PH early in life. It also introduces a class of ‘multifactorial PH’ because—especially in children—often more than one factor may account for the diagnosis of PH. The main aim was to provide a system that is clinically useful, incorporates specific paediatric aspects that were previously not adequately addressed and allows categorising complex patients with a multifactorial pathogenesis of their PH accordingly ([table 3](#)).

EPIDEMIOLOGY

Data on the exact incidence and the prevalence of PH in infancy and childhood are sparse. PH in childhood is seen with a variety of conditions, however, if at all, limited data are mainly available for IPAH and PH associated with CHD (PH-CHD). Two Dutch nationwide registries of paediatric PH suggested an annual incidence of 0.7 cases per million children for IPAH and a point prevalence of 4.4 per million children. For PH-CHD, annual incidence and prevalence were 2.2 and 15.6 cases per million children, respectively. Compared with adult studies, the incidence of IPAH seems to be lower in children, whereas PH-CHD may occur more frequently in childhood.⁹ Data from the UK Pulmonary Hypertension Service reported a slightly lower incidence for IPAH, that is, 0.48 cases per million children per year for IPAH and a prevalence of 2.1 cases per million children (IPAH).¹⁰ A 5-year multicentre prospective study including 21 referral centres in France reported an estimated prevalence of 3.7 paediatric PAH cases per million, and for IPAH, 2.2 cases per million.¹¹

All in all, based on the available data a PH prevalence in 2–16 per million children can be estimated, acknowledging that there are risk groups in whom occurrence of PH in childhood and adolescence is substantially higher. This includes, for example, schistosomiasis,² and probably other unrecorded, underserved children in developing countries with left heart

Table 1 Recommendations on diagnosis, monitoring and outpatient care in children with suspected or confirmed PH/PPHVD

Recommendations	COR	LOE
Children with suspected or confirmed PH/PPHVD should be referred to, comprehensively evaluated and treated in multidisciplinary, specialised paediatric centres.	I	C
The initial evaluation should include a comprehensive medical history, thorough physical examination, assignment to a functional class and formal assessment of cardiac function (ECG and echocardiogram). This should be followed by further diagnostic testing to delineate the PH aetiology—ideally prior to the initiation of therapy.	I	B
A CXR is recommended at baseline with acceptable risk/radiation exposure.	I	B
Regular CXRs at follow-up are not indicated, unless there is a clinical reason.	III	B
Serial echocardiograms and ECGs are recommended every 3–6 months. In unstable or symptomatic patients or those who undergo therapeutic changes, more frequent echocardiograms may be indicated.	I	B
Further imaging is recommended to exclude underlying parenchymal lung disease, pulmonary veno-occlusive disease, CTEPH and anatomical obstructions, which may be beyond what can be diagnosed by routine transthoracic echocardiography.	I	C
If CTEPH is suspected, and a definite diagnosis is still pending despite exhaustion of other imaging modalities (cardiac catheter, chest CT), a ventilation-perfusion (VQ) scan can be useful for selected patients.	IIa	C
If no underlying cause of the PH is evident, an abdominal ultrasound is indicated to rule out liver cirrhosis and/or portal hypertension.	I	C
A sleep study (polysomnography) should be performed in patients with PH at risk for sleep-disordered breathing, especially patients with Trisomy 21, other syndromes or patients with significant daytime sleepiness.	I	B
In PH patients who are not particularly at risk for sleep-disordered breathing but have an inadequate response to PAH-targeted pharmacotherapy, a sleep study is recommended and can provide additional information.	I	B
Serial CPET (treadmill, bicycle) and the 6MWT are recommended to assess and monitor exercise tolerance, gauge prognosis and for surveillance of therapy in children with PH of an appropriate age.	I	B
Pulse oximetry during CPET/6MWT is helpful to allow shunt detection especially in patients with PAH-CHD.	IIa	C
Blood gas analysis in paediatric PH patients can be useful at rest, at ventilatory threshold and at maximal exercise during CPET. If available, analysis should include haemoglobin and lactate.	IIa	C
A basic lung function test (ie, body plethysmography) should be performed at the time of diagnosis to rule out any coexisting airway disease/lung disease (obstructive, restrictive and combined), which may need to be addressed independently to targeted PH therapy.	I	C
In children with end-stage disease, timely referral to and discussion with a transplant centre should be sought, if lung transplantation represents a considerable option for the individual patient.	I	C
For children with PH/PPHVD undergoing surgery or other interventions requiring sedation or general anaesthesia, consultation with cardiac anaesthesia and the PH service, and appropriate postprocedure monitoring is required.	I	C
Good communication between teams, awareness of the severity of the disease, timely preparation (including 'standby' of inhaled nitric oxide) and conscious anaesthetic strategies maintaining an adequate systemic vascular resistance and adequate preload are recommended to reduce morbidity as well as fatal events.	I	C
Female adolescents with PH/PPHVD should undergo timely counselling regarding the significant maternal and fetal pregnancy risks and options for secure contraception.	I	B
Paediatric patients with PH in the high-risk category should not participate in competitive sports.	I	C
It is recommended that children with mild to moderate PH/PPHVD should engage in light to moderate aerobic activity, but be allowed to self-limit their activities as required.	I	C
Children with PH should avoid strenuous and isometric exercise, as well as dehydration.	I	C
It is recommended that children with PH should only fly on commercial airplanes in a stable and compensated condition.	I	C
Children with PH should undergo all recommended routine vaccinations to prevent any deteriorations due to avoidable infections.	I	C
RSV (<2 years of age), pneumococcal and influenza vaccinations should be administered in paediatric PH patients if no contraindications exist.	I	C

6MWT, 6 min walk test; CHD, congenital heart disease; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic disease; CXR, chest X-ray; PAH, pulmonary arterial hypertension; PH, pulmonary hypertensive; PPHVD, paediatric pulmonary hypertensive vascular disease; RSV, respiratory syncytial virus.

Table 2 Classification of pulmonary hypertension (5th World Symposium on Pulmonary Hypertension, Nice 2013)⁵

1. Pulmonary arterial hypertension (PAH)	
1.1. Idiopathic PAH	
1.2. Heritable PAH	1.2.1. BMPR2 1.2.2. ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3. Unknown
1.3. Drug and toxin induced	
1.4. Associated with:	1.4.1. Connective tissue disease 1.4.2. HIV infection 1.4.3. Portal hypertension 1.4.4. Congenital heart diseases 1.4.5. Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	
1'' Persistent pulmonary hypertension of the newborn	
2. Pulmonary hypertension due to left heart disease	2.1. LV systolic dysfunction 2.2. LV diastolic dysfunction 2.3. Valvular disease 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia	3.1. Chronic obstructive pulmonary disease 3.2. Interstitial lung disease 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4. Sleep-disordered breathing 3.5. Alveolar hypoventilation disorders 3.6. Chronic exposure to high altitude 3.7. Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension	
5. Pulmonary hypertension with unclear multifactorial mechanisms	5.1. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy 5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertensive

disease leading to pulmonary venous hypertension, i.e. group 2 PH, for example, rheumatic heart disease (with mitral stenosis).

DIAGNOSTIC ALGORITHM

Ideally, children with suspected or confirmed PH should be referred to, comprehensively evaluated and treated in multidisciplinary, specialist paediatric PH centres. The full assessment of invasive haemodynamics (right and left heart catheterisation), including ventricular performance and advanced non-invasive imaging, should be performed prior to the initiation of therapy by means of echocardiography,⁷¹ cardiac catheterization⁷² and cardiac MRI.⁷³

However, the clinical status of the patient at the time of presentation has to be taken into account and stabilisation of the patient is paramount, even if this includes initiation of advanced PH-specific therapies before exact diagnosis.

In the process of the initial evaluation of 'pulmonary hypertension' and work-up, both a comprehensive medical history and physical examination are mandatory. Particular attention

Table 3 Panama classification of Paediatric Pulmonary Hypertensive Vascular Disease (PPHVD) (2011): 10 basic categories of PPHVD

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

From Cerro *et al.*⁴

should be paid to accompanying symptoms and problems that could potentially suggest an underlying cause or modifier of PH (eg, prematurity— chronic lung disease; Raynaud's phenomenon—systemic sclerosis, systemic lupus erythematoses; Down syndrome—abnormal sleep study).

The diagnosis of IPAH can only be made after exclusion of other known factors playing a causative role in the pathobiology of PH applying a combined diagnostic approach for PH evaluation.

Basic diagnostics should include determination of the functional class (FC) of the child or adolescent (table 6). Further investigations, such as ECG, chest X-ray (CXR), echocardiography and functional testing (if feasible in that age), that is, lung function test, 6 min walk (6MWT) and cardiopulmonary exercise testing (CPET), should also be performed at the initial evaluation for PH.

Symptoms and clinical signs

Symptoms in PH are highly variable in individual patients and are often 'non-specific'.^{5 12} During infancy and younger childhood, clinical presentation with overt right heart failure is extremely rare. Symptoms at rest (ie, WHO FC 4) are only present in very advanced disease. Young children may present with failure to thrive, school-age children often present with exercise-induced dyspnoea or dyspnoea at rest, syncope or chest

Table 4 Symptoms and clinical signs of pulmonary hypertension

Clinical signs	Symptoms
RV heave	SOB
Active precordium	SOB on exercise
Accentuated P2	Fatigue/tiredness
Pansystolic murmur (TR)	Exercise intolerance
Diastolic murmur (PR)	Dizziness/syncope
JV distension	Chest pain/angina
Abdominal distension/hepatomegaly	Visible neck veins
Peripheral oedema	Abdominal distension
Ascites	Oedema
Cool peripheries	

SOB; shortness of breath.

Table 5 WHO functional classification of pulmonary hypertension

Description of functional assessment classification	
Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class II	Patients with PH resulting in <i>slight</i> limitation of physical activity. They are comfortable at rest. <i>Ordinary physical</i> activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class III	Patients with PH resulting in <i>marked</i> limitation of physical activity. They are comfortable at rest. <i>Less than ordinary activity</i> causes undue dyspnoea or fatigue, chest pain or near syncope.
Class IV	Patients with PH with <i>inability to carry out any physical activity without symptoms</i> . These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Reprinted from Rubin.⁶⁸
PH, Pulmonary hypertension.

pain.¹³ The diagnosis of PH may also be the result of coincidental findings (eg, increased cardiothoracic ratio on CXR, ECG abnormalities). Occasionally, children may be misdiagnosed with a bronchial illness or asthma. Possible clinical signs and symptoms at presentation in a child with PH are listed in table 4.

Physical examination should include the assessment of growth (percentiles on chart) in order to address any nutritional problems. Four limb blood pressure as well as four limb transcutaneous oxygen saturation (SaO₂) should be obtained on initial assessment to detect any aortic arch/obstruction issues (eg, coarctation of the

aorta), hypoxaemia or even differential cyanosis (eg, patent ductus arteriosus with predominant right-to-left shunt).

Functional classification

Functional classes (FC) are used to categorise patients into groups with comparable clinical status and disease-related compromise. FC often correlates with morbidity, quality of life and risk of death.¹⁴ The two most frequently employed functional classification schemes are the WHO and the New York Heart Association classification (table 5).^{15 16}

Functional classifications are, however, not without problems, particularly in young children and children with handicaps (eg, Trisomy 21).

Therefore, a uniform, comprehensive and applicable classification with easily to determine variables would be desirable. The PVRI Paediatric Workforce recently suggested a specific functional classification system for different age groups, implementing factors such as the ability to thrive, developmental milestones and attendance of nursery/school (table 6).¹⁷ While promising, this newly suggested functional PH classification awaits external validation and correlation with paediatric outcome data. Despite the pitfalls using any functional classification, WHO FC evolved as one of few convincing prognostic factors in a recent meta-analysis.¹⁸

ECG

Right axis deviation beyond infancy (exceptions may exist in certain patients with PH-CHD), signs of right atrial dilatation, RV hypertrophy or strain, and significant intraventricular

Table 6 Paediatric functional classification of pulmonary hypertension

Age functional class	0–0.5 years	0.5–1 years	1–2 years	2–5 years	5–16 years
I	Asymptomatic, growing along own centiles and developing normally, no limitation of physical activity Gains head control and increases body tone from 0 to 3 months, then rolls over and has no head lag. Sitting with support				
		Mobile, sitting, grasping, starting to stand, crawling, playing	Standing, starting to walk/walking, climbing	Regular school/nursery attendance, playing sports with his/her classmates	
II	Slight limitation of physical activity, unduly dyspnoeic and fatigued. Falling behind physical developmental milestones/delayed physical development. Comfortable at rest. Continues to grow along own centiles				
				Nursery/school attendance 75% normal. No chest pain	
IIIa	Marked limitation of physical activity, unduly fatigued. Regression of learned physical activities. Comfortable at rest. Less than ordinary activity causes undue fatigue or syncope and/or pre-syncope (or chest pain) Quiet and needs frequent naps. Growth compromised. Poor appetite. Requires excessive medical attention				
		Hesitant and unadventurous. Stops crawling	Reluctant to play	Nursery/schooling compromised, <50% normal attendance Not climbing stairs, reluctant to play with friends No attempt at sports	
IIIb	Growth severely compromised. Poor appetite. Supplemental feeding. Less than ordinary activity causes undue fatigue or syncope (or chest pain). Plus features of Class IIIa				
				Unable to attend nursery/school, but mobile at home. Wheelchair needed outside home	
IV	Unable to carry out any physical activity without undue dyspnoea, fatigue or syncope (or chest pain), not interacting with family. Syncope and/or right heart failure. Plus features of class III				
				Unable to attend nursery/school, wheelchair dependant, not interacting with friends	

Modified from Lammers et al.¹⁷

conduction delay can already provide important clues on the presence but not the severity of PH.

In patients with IPAH, RV hypertrophy was present in 87% and right axis deviation in 79% of patients on ECG.¹⁹ Due to the physiological right axis in younger children, this parameter is less reliable in infancy and in young children. A normal ECG for age, however, does not exclude the presence of PH.

Ventricular arrhythmias are rare in PH, but supraventricular tachycardias may occur. Atrial flutter or fibrillation may also be seen in advanced stages of paediatric PH.²⁰ In PH patients with Eisenmenger syndrome, the occurrence of arrhythmia is thought to be associated with a poor prognosis.²¹

Taken together, for diagnosis, follow-up, decision-making or guidance of therapy, the ECG can be helpful; however, it cannot serve as a screening tool in isolation due to the limited sensitivity and specificity. However, given the easy access, low cost and wide availability, an ECG should be undertaken every 3–6 months.

CXR imaging

Ninety percent of adult patients with IPAH have an abnormal CXR at the time of diagnosis.¹⁹ Typical findings on CXR may be central pulmonary artery dilatation, pruning (suggestive of loss of peripheral blood vessels), as well as right atrial and RV enlargement in advanced cases.

A CXR usually allows to reasonably exclude moderate-to-severe lung disease or pulmonary venous hypertension due to left heart disease, leading to pulmonary oedema. However, the degree of PH does not necessarily correlate with the extent of radiographic abnormalities. In children with suspected PH, a CXR provides useful baseline information with acceptable risk/radiation exposure. Regular CXRs at follow-up are not indicated, unless there is a specific clinical indication (such as an underlying parenchymal lung disease).¹⁵

Echocardiography

While the definition of PH is still based on invasive haemodynamic measures, obtained by cardiac catheterisation, the first diagnostic tool and modality in suspected PH is generally the transthoracic echocardiogram.⁷¹

Echocardiography does not only allow a comprehensive initial assessment of cardiac anatomy, dimensions and function of both ventricles; it may also confirm the suspicion of elevated pulmonary pressures and usually allows for the quantification and estimation of those. Central venous pressure can be roughly estimated and functional parameters of RV and LV strain, contractility and ventriculo-ventricular interactions can be assessed.²²

Despite the recognised limitations of echocardiography, to date it remains the imaging modality of choice that currently appears to be the most appropriate tool for longitudinal assessment of PH in children due to its non-invasiveness, wide availability and relative cost-effectiveness. Further details of a standardised approach including recommended parameters for the assessment of PH are discussed in greater detail in a dedicated article in this issue.⁷¹

Serial echocardiograms and ECGs are recommended every 3–6 months. In unstable or symptomatic patients or those who undergo therapeutic changes, more frequent echocardiograms may be indicated.

Lung function tests

In children old and mature enough to reliably cooperate, a basic lung function (or body plethysmography) test should be

performed at the time of diagnosis. This is to rule out any underlying or coexisting airway or parenchymal disease (obstructive, restrictive or combined), which may need to be addressed independently from targeted PH therapy and warrant other treatment modalities. Static and dynamic parameters should be obtained, assessing presence and degree of restrictive or obstructive disease.

In patients with significant obstructive airway disease, symptomatic relief may be obtained from additional bronchodilator treatment. Furthermore, it is important to minimise respiratory comorbidity and avoid air trapping, consolidation or atelectasis, which often results in significant V/Q mismatch. The latter can negatively affect the underlying pathophysiology of PH aggravate PH-associated symptoms and hence contribute to confirm the severity of PH.

The presence of significant restrictive lung disease warrants a more detailed search for respiratory diseases involving the lung parenchyma and rule out interstitial lung disease, pulmonary veno-occlusive disease (PVOD) or pulmonary capillary haemangiomas (PCH), treatment of which may differ from advanced PH therapy; pulmonary vasodilator therapy can actually have adverse effects and may be contraindicated in PCH and PVOD.^{23 24}

In addition, certain drugs (eg, inhaled iloprost) have been shown to cause bronchospasm in some children, and thus, a lung function test should be performed prior to the start of any inhalative PH therapy.²⁵

6MWT and CPET

Serial CPET (treadmill, bicycle) and the 6MWT are recommended to assess and monitor exercise tolerance, gauge prognosis and for surveillance of therapy in children with PH of an appropriate age. Objective measures can be obtained and can be compared against normal values of healthy peers.

Unlike formal CPET, a 6MWT can be reliably performed from a young age (school children) onwards. Thus 6MWT represents an assessment tool for a wide age spectrum of patients. The 6MWT offers technical advantages versus CPET as it is easily applicable, does not require any expensive equipment and is less time consuming than a standardised CPET.

Box 2 Standardised cardiopulmonary exercise testing ramp protocol (sitting ergometer)

- ▶ 3 min rest on the ergometer
 - ▶ 3 min warm-up with unloaded cycling (friction only), constant pedalling rate 60–70 min⁻¹
 - ▶ Constant increase in work rate to exhaustion
 - Should be achieved in 8–12 min
 - Estimated from previous tests, body mass and anamnestic data:
 - Increase 5 W/min in very small children and severely disabled patients
 - Increase 10 W/min in patients with pulmonary hypertension (PH) and less affected children
 - Increase 15 W/min in very fit patients with PH
 - Increase 20–50 W/min in healthy adolescents and adults
 - ▶ 3 min cool down with little load (about 1/10 of max. work load)
 - ▶ At least another 2 min arrhythmia surveillance
- From Cooper and Weiler-Ravell.²⁸

Advantages of CPET include the greater variety of physiological measures, particularly additional information about respiratory capacity. In children with PH who are less compromised, routine CPET should be considered for an objective evaluation of their exercise capacity.²⁶

During CPET, the following parameters should be obtained and have proven to be useful monitoring patients with PH: peakVO₂, peak blood pressure and the ventilatory equivalent of CO₂ (VE/VCO₂ measured at ventilatory threshold or as slope) are of predictive value for survival and hospital admission. VE/VCO₂-slope, which can be derived from submaximal exercise testing, has been shown to correlate with disease severity and mortality in a paediatric cohort with PH.²⁷

In children with PH who still have a relatively preserved exercise capacity (eg, walking distance >300 m), there is no good correlation of 6MWT distance with peakVO₂, while CPET provides a more accurate estimation of cardiopulmonary limitations to exercise capacity. However, in children whose 6MWT is <300 m, peak VO₂ correlates well with the distance walked. 6MWT may, therefore, actually serve as a test of maximal exercise in children with a greater degree of exercise intolerance.²⁶ **Box 2** outlines a standardised CPET ramp protocol for a sitting ergometer.²⁸ For a comprehensive review of exercise testing in children with cardiac disease, see reference.²⁹

Sleep study (polysomnography)

Patients with a suspicion or a predisposition for a breathing disorder (eg, patients with Down syndrome or with relevant daytime sleepiness, hypertrophic adenoids) and especially those with an inadequate response to PH-targeted pharmacotherapy should undergo a formal sleep study, which could provide additional information and may have direct therapeutic implications.^{30–31} Nocturnal CO₂ retention does not only impact on the subjective well-being of the patient and functional capacity during daytime but may also aggravate PH/PHVD. If a sleep study is positive, appropriate measures such as counselling, the use of a sleeping mask or adenoidectomy in selected cases should be considered.³²

High-resolution chest CT /CT angiography

Advanced chest CT imaging is recommended to exclude underlying parenchymal lung disease, PVOD, chronic thromboembolic pulmonary hypertension (CTEPH) and anatomical obstructions (eg, peripheral pulmonary stenosis or pulmonary venous stenosis), which may be beyond the diagnostic scope of routine transthoracic echocardiography.

A chest CT angiography is recommended in the initial assessment of children with suspected PH. However, if an obvious cause for PH/PHVD exists (eg, a large left-to-right cardiac shunt), these advanced imaging modalities associated with considerable costs and radiation may be omitted. A chest CT is the assessment modality of choice if parenchymal lung disease is suspected on CXR. In addition, a chest CT angiography is indicated in every patient being evaluated for lung transplantation.³³

Cardiac catheterisation and cardiac MRI

A cardiac MRI (cMRI) study should be considered in children with suspected PH/PHVD as part of the initial diagnostic evaluation and during follow-up to assess changes in ventricular function, mass and volumes (chamber dimensions) in case it can be performed without sedation/anaesthesia. If sedation/anaesthesia is needed, the risk of sedation/anaesthesia needs to be balanced against the potential gain of information of the cMRI study and its impact on the future therapy of the individual patient with

PH. In our experience, the risk of sedation/general anaesthesia is higher in patients with severe disease (history of pulmonary vascular crisis, syncope, high PVR, WHO FC 3–4) and those without a RV decompressing shunt e.g., IPAH.

Due to the important therapeutic implications, the complexity and specific risks and benefits of the procedures, separate articles in this issue are dedicated to cMRI⁷³ and cardiac catheterisation⁷² including acute vasodilator testing.^{34–39}

Ventilation/perfusion lung scan (V/Q scan)

A V/Q lung scan is more sensitive than CT in detecting peripheral thromboembolic disease, and thus, in adults, it is the method of choice to rule out potentially treatable CTEPH.⁴⁰ Because CTEPH has a very low incidence in children compared with adults,⁴¹ a V/Q scan should only be considered in children when there is suspicion for the presence of CTEPH rather than using this method as a screening tool. However, if a definite diagnosis is still uncertain after exhaustion of other imaging modalities (cardiac catheterisation, high-resolution chest CT (HRCT)), a V/Q scan can be useful for selected patients.⁴²

Abdominal ultrasound

Porto-pulmonary hypertension in childhood is rare;⁴³ however, if no underlying cause of the PH/PHVD is evident, an abdominal ultrasound is indicated to rule out liver cirrhosis and/or portal hypertension. The use of contrast agents and colour Doppler have been reported to improve diagnostic accuracy in adults.^{43–46}

Laboratory and immunological screening tests

It is unclear which laboratory tests are particularly useful in the diagnostic work-up of PH/PHVD in children as data are sparse: **table 7** provides an overview of routine blood tests, which should be considered for the diagnostic work-up of adolescent and adult patients with PH at first presentation. For children, it appears reasonable to be more selective and to take the ethnic background, travel history and to accompanying symptoms into account. For example, although schistosomiasis is a frequent cause of PH worldwide, it is probably not necessary to test for it in most European children (**table 7**).^{42–47}

Genetic testing

Genetic counselling and testing is recommended for families with children with IPAH or HPAH. HPAH patients' family members who develop new cardiorespiratory symptoms should be evaluated immediately for PAH.

For further details on comprehensive biomarker and genetic testing, please see the dedicated article in this issue.⁷⁴

Diagnostic algorithm

The Tracking Outcomes and Practice in Paediatric Pulmonary hypertension (TOPP) registry investigators reported that to date, in the majority of children with PH, the current diagnostic work-up recommended for adults are not followed (**figure 1**). This finding highlights that adult guidelines do not appropriately meet the demands of a thorough work-up tailored for children and/or probably a lack of awareness of existing guidelines for adults.^{2–38}

If PH/PHVD is severe and the patient presents severely ill in overt heart failure and/or pulmonary vascular crisis, cardiac catheterisation may be postponed due to its inherent risks and pharmacotherapy including intravenous prostanoids started immediately.^{72–75} Assessment may be postponed until the patient is clinically stabilised. A separate article in this issue

Table 7 Overview of routine laboratory blood tests in paediatric pulmonary hypertension

Diagnostic test	Aim	Comment
Full blood count*	Anaemia, polycythaemia	
BNP/NT-proBNP*	Detect ventricular dysfunction/heart failure	May be useful for longitudinal follow-up/response to treatment
Iron studies (free iron, transferrin, ferritin and iron-binding capacity)*	Iron deficiency	Supplementation Nutritional counselling Regular testing in patients with PH-CHD and cyanosis
Vitamin B12, folic acid*	Vitamin B12 or folic acid deficiency	Supplementation, malabsorption Nutritional counselling
Urea and electrolytes including uric acid*		
Liver functional enzymes (GOT, GPT, GGT, LDH)*	Exclude liver dysfunction	Every 4–12 weeks when stable on ERA therapy
Clotting* (PTT, INR, prothrombin, D-dimers)		
Hepatitis serology†		
Thyroid function test†		
CK, CK-MB; troponin†		
HIV†	Causative factor for PH	ELISA
ANAs (anticentromer antibodies, anti-SM, dsDNA, anti-Ro U1-U2 RNP, B23, Th/To)†	? connective tissue disease, systemic sclerosis	
Anticardiolipin antibodies† Lupus anticoagulant†	Lupus erythematoses, peripheral pulmonary embolic disease	
Thrombophilia screening, including anti-phospholipid antibodies	Suspicion of CTEPH Antiphospholipid syndrome	
Immunoassay/PCR	Schistosomiasis	Consider if appropriate medical history
Hb electrophoresis	Rule out haemoglobinopathy, eg, sickle cell disease/ thalassaemia	Consider if ethnic risk group

*Recommended at presentation in all patients.

†May be useful for selected patients, unmarked decision on an individual patient basis.

BNP, brain-natriuretic peptide; CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonists; PH, pulmonary hypertension.

discusses cardiac catheterisation and vasodilator testing in greater detail.⁷²

Screening for paediatric PH is performed by ECG and echocardiography at the discretion of and after discussion among the primary paediatrician and paediatric cardiologist. If these investigations suggest the presence of PH/PHVD, CXR and HRCT should be considered.

Results from the TOPP registry revealed that ECG, echocardiography and CXR were the most frequently non-invasive tests used in the diagnostic work-up of children with PH. Of 456 patients included, none of them had all three tests considered normal, indicating a possible strength of combining these non-invasive tests to rule out PH with a reasonable degree of certainty.³⁸ Once the combination of ECG and echocardiography points to the diagnosis ‘PH’, cardiac catheterisation, biomarker testing (NT-proBNP or BNP) and other tests should be performed, as outlined in table 7.

The TOPP registry revealed that once the diagnosis ‘PH’ was established, in <25% of children BNP and NT-proBNP testing was performed. 6MWT and CPET were conducted in only 38% and 7%, respectively.³⁸

Finally, (combined right and left) cardiac catheterisation should be performed in all forms of significant PH (i) to confirm diagnosis and to distinguish between (ii) PH without elevated PVR and PH with elevated PVR (=PPHVD), (iii) pre-capillary from post-capillary PH/PPHVD, and (iv) to determine right atrial pressure, as well as RV and LV end-diastolic pressures as surrogate for diastolic function. Patients with PAH at diagnosis (and selectively at follow-up) need to undergo pulmonary vasoreactivity testing (for according recommendations, see article on cardiac catheterisation).⁷²

If basic investigations including cardiac catheterisation,⁷² confirm the diagnosis of PH/PHVD, treatment should be initiated and an appropriate follow-up plan should be made for the individual patient.⁷⁶

MONITORING AND OUTPATIENT CARE

Table 8 shows an overview of investigations and tests that are recommended at the time of diagnosis and during follow-up, as well as additional optional tests that should be considered on an individual basis. Depending on clinical status, outpatient follow-up visits in 3-month to 6-month intervals appear

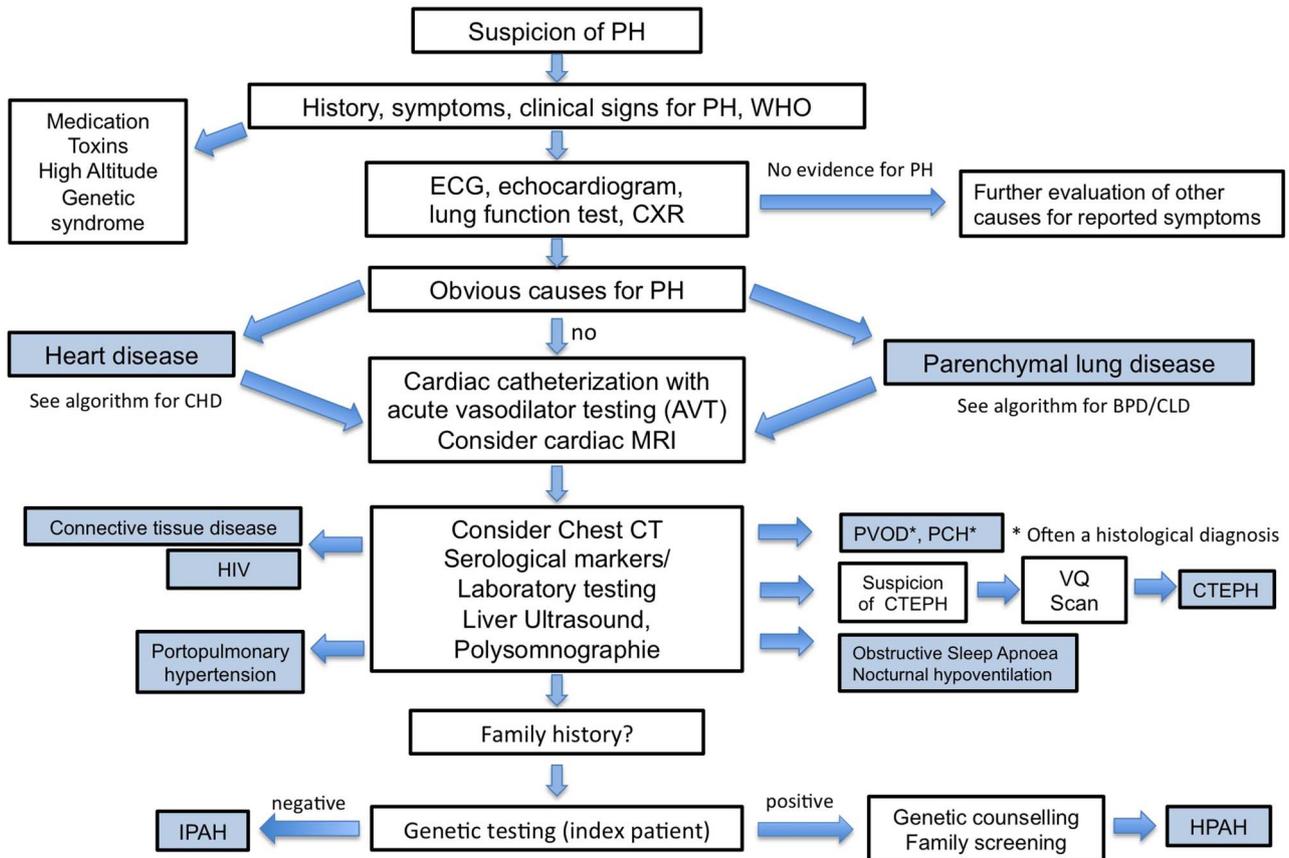


Figure 1 Diagnostic algorithm for a child or adolescent with suspected pulmonary hypertension. CHD, congenital heart disease; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; CXR, chest X-ray; HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; LFT, liver function test.

reasonable. More frequent visits may be indicated in patients with progressive, advanced or end-stage disease, or after initiation or significant changes in therapy.

Patients on intravenous or subcutaneous prostanoid therapy should be seen at least every three months,^{48–49} whereas stable patients on oral (combination) therapy can be seen at 6-month intervals.

Some advanced therapies (eg, endothelin receptor antagonists) warrant further visits for laboratory testing.⁷⁶

During every outpatient visit, a thorough history should be sought, and changes or occurrence of new clinical symptoms should be evaluated. Patients' functional status and potential change of FC should be documented. Depending on children's age, maturity and cooperation, physical functional testing such as 6MWT and/or CPET should be performed in 6-month to 12-month intervals.

Elective surgery/general anaesthesia

Elective procedures under general anaesthesia require careful consideration of the underlying indication and judgement of the risk–benefit ratio as any general anaesthesia bears a substantial high risk for a child with moderate to severe PH. If a potential benefit of the procedure (gain of information) outweighs the estimated risk, or the surgery/intervention is unavoidable, timely planning is required. Management by an experienced anaesthesiologist who is familiar with PH haemodynamics and the involved pitfalls should be facilitated.

Good communication between teams, awareness of the severity of the disease and risks, and timely preparation are

recommended. Conscious anaesthetic strategies maintaining an adequate systemic vascular resistance and adequate preload, and appropriate postprocedure monitoring are crucial to reduce morbidity and fatal procedure-related events.^{50–52}

Pregnancy/Contraception

Pregnancy has a very high risk of fatal outcome for a pregnant woman with PH (30–50%) and for the fetus, and in the majority of cases, the caring physician will recommend termination of pregnancy. Female adolescents with PH/PPHVD should undergo timely counselling regarding options for secure contraception.^{53–54}

Physical education and exercise

CPET testing is recommended for children with mild to moderate PH/PPHVD prior to engaging in any recreational or athletic activities.

It is recommended that children with stable mild to moderate PH/PPHVD should engage in light to moderate aerobic activity but be advised to self-limit their activities as required, avoid strenuous exertion and dehydration.

Paediatric patients with severe PH (FC III or IV and/or systemic or supra-systemic PA pressure) and/or recent history of syncope carry a high risk of sudden cardiac death with exercise and thus should not participate in any (competitive) sports.

Flying on commercial airplanes

Data on children exposed to cabin pressures and evaluation of need for supplemental oxygen are lacking. Generally, it is recommended that patients with PH should only fly on commercial

airplanes in a stable and compensated condition. For patients with advanced disease, systemic pulmonary artery pressures and/or impaired ventricular function, it appears reasonable to use supplemental oxygen during the flight to minimise hypoxic vasoconstriction. The ESC and European Respiratory Society guidelines for PH recommend in-flight supplemental oxygen for patients with PH in FC III or IV and those with arterial partial oxygen pressure consistently <8 kPa (60 mm Hg).^{42 55}

The PH patients' caregivers should contact the airline in advance regarding the availability of supplemental oxygen in sufficient amounts during airline transport.

Vaccinations/Care of central intravenous lines

Children with PH should be under shared care and should be primarily seen and linked to a local paediatrician as first line of contact for all regular childhood investigations, routine vaccinations and general medical problems. However, good proactive

communication and close cooperation is mandatory between specialised physicians seeing the patient with a PH focus and local community teams. Paediatricians should be actively encouraged to contact PH physicians for advice, for example, seeking support for and planning minor procedures, not necessarily related to the PH itself, where the patient could be exposed to any excessive risk (eg, general anaesthetic for dental procedure).

Children with PH should undergo all recommended routine vaccinations to prevent avoidable infections. Respiratory syncytial virus (<2 years of age), pneumococci and influenza vaccinations should be administered in paediatric PH patients if no contraindications exist.

Antibiotic prophylaxis for the prevention of subacute bacterial endocarditis is nowadays reserved for special patient subgroups (eg, cyanotic patients).⁵⁶

In patients with a permanent central venous access (eg, for the administration of continuous prostacycline analogues), the

Table 8 Recommended tests/investigations at diagnosis and follow-up of a child or adolescent with pulmonary hypertension/pulmonary hypertensive vascular disease

Test/investigation	At first presentation/diagnosis	Follow-up outpatient visits			Comment
		3–6 monthly intervals	Every 12 months	Elective testing when indicated	
Comprehensive medical history/interim history	•	•			
Assignment to functional class	•	•			
Growth variables (centiles)	•	•			
Physical examination	•	•			
Four limb blood pressure	•				
Pulse oximetry both arms/one leg	•	•			
Electrocardiogram	•	•			
Transthoracic echocardiogram	•	•			
Chest X-ray	•			•	
Lung function test/body plethysmography	•			•	
6 min walk test	•	•			
Cardiopulmonary exercise test	•		•		
Laboratory testing	•			•	According to drug treatment
NT-proBNP or BNP	•	•		•	
Cardiac MRI*	•			•	*MRI at diagnosis or first presentation; indication should be discussed on an individual patient basis
Comprehensive right and left heart catheterisation (including full pulmonary vasoreactivity testing)	•			•	
(High resolution) chest CT/CT angiogram*	•			•	* Diagnostic value of a pulmonary angiogram to be discussed on an individual patient basis
Polysomnography				•	
Ventilation/perfusion scan				•	

BNP, brain-natriuretic peptide.

caregivers must be vigilant for possible line infections. If clinically suspected (eg, unexplained fever, erythema or other infectious signs around line entry site), the continuous infusion of the prostanoid must *not* be abruptly disconnected. Due to the short half-life, the prostanoid has to be transitioned to a peripheral venous access, while the infusion via the central line is carefully weaned. Transition should ideally take place in a stepwise manner with monitoring of the clinical status, saturation and blood pressure of the patient, before blood cultures can be withdrawn from the central line. However, if line infection is confirmed, the chance to permanently clear the existing central line is often unsuccessful, despite antibiotic treatment. Most patients require removal of the infected line and alternative central line placement. Ideally, replacement should take place after a few days of antibiotic treatment and control of systemic infection/bacteraemia to avoid instant contamination of the new central line. The same technical process applies to patients with a leaking line or line dysfunction. They need to be transferred to the next emergency department immediately for intermittent peripheral intravenous line placement to ensure continuation of prostanoid therapy (epoprostenol has a very short drug half-life).

School

Close contact to healthcare providers and teachers at school should be sought. The aim is to familiarise them with practicalities of supporting a chronically ill child, to allow for a (near-) normal school attendance, to maximise pupils' integration and to address understandable concerns and anxieties of the educators. Arrangements at school have to be made to facilitate the application/intake of any medication required during school hours (eg, inhaled iloprost, oxygen).

Additional interventional and surgical therapies

Atrial septostomy is often considered as the last option before active listing for bilateral lung transplantation. Indeed, atrial septostomy should represent a conscious step of active PH management particularly in patients with syncope.⁵⁷ Paediatric experience is available and describes clinical improvement and abolishment of syncope, albeit an associated procedural risk, has to be acknowledged particularly for patients with increased right atrial pressures.⁵⁸

Lately other surgical measures (Potts shunt) and interventional procedures (ductal stenting) have been introduced and offered to small numbers of patients.⁷⁶ Paediatric experience is sparse and measures may be discussed as compassionate care. A detailed discussion of the involved risks and benefits is beyond the scope of this article; however, further details can be found in references.^{59–62 76}

Lung transplantation

For some children, bilateral lung transplantation may be an option. However, despite improved immunosuppression regimens, overall survival after lung transplantation remains limited compared with other solid organ transplantation.

Median survival following paediatric lung transplantation is reported to be 4.9 years (2013 International Society of Heart and Lung Transplantation guideline).^{63 64} Acute rejection and bronchiolitis obliterans syndrome remain a major clinical problem responsible for both morbidity and mortality.⁶⁵ Open counselling is important to balance risks and benefits and gauge whether this is a desirable and realistic option for each individual patient and their families. In patients with end-stage PHVD,

early referral and evaluation by an interdisciplinary paediatric transplant centre should be sought.^{65–67}

Palliative care

As disease progresses, it is important to support patients and families beyond providing high-quality medical care. Regardless of the decision to be actively listed for bilateral lung transplantation in end-stage disease, the extent of intensive care support should be discussed in a timely manner and alternatives, for example, palliative care, should be offered. Additional psychological support for families and patients and contact to professional social networks may be helpful.

General support

Children, siblings and caregivers of paediatric patients with PH/PHVD should be assessed for psychosocial stress and be readily provided psychosocial support and referral to appropriate institutions as needed. Individualised recommendations should be made, dependent on the underlying cause of the child's PH and clinical status. Participation in physical education classes, access to education facilities and supporting aids (eg, wheelchair) to maintain mobility for patients with advanced disease should be discussed on an individual basis to meet the patients' and families' needs.

CONCLUSION

Due to the relatively low prevalence of PH/PHVD in childhood, the complexity of the disease, the heterogeneity of presentation and disease progression, and the need of a multidisciplinary approach, patient care and follow-up should take place at dedicated PH centres. In the setting of progressing disease and over time increasingly compromised patient with PH/PHVD, a balance has to be sought between regular visits at specialist PH clinics and good competent support from local medical teams, and palliative care services close to the patient's home.

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