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CONSENSUS STATEMENT

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

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The European Pediatric Pulmonary Vascular Disease Network is a registered, non-profit organization that strives to define and develop effective, innovative diagnostic methods and treatment options in all forms of pediatric pulmonary hypertensive vascular disease, including pulmonary hypertension (PH) associated with bronchopulmonary dysplasia, PH associated with congenital heart disease (CHD), persistent PH of the newborn, and related cardiac dysfunction. The executive writing group members conducted searches of the PubMed/MEDLINE bibliographic database (1990−2018) and held face-to-face and web-based meetings. Ten section task forces voted on the updated recommendations, based on the 2016 executive summary. Clinical trials, meta-analyses, guidelines, and other articles that include pediatric data were searched using the term "pulmonary hypertension" and other keywords. Class of recommendation (COR) and level of evidence (LOE) were assigned based on European Society of Cardiology/American Heart Association definitions and on pediatric data only, or on adult studies that included >10% children or studies that enrolled adults with CHD. New definitions by the World Symposium on Pulmonary Hypertension 2018 were included. We generated 10 tables with graded recommendations (COR/LOE). The topics include diagnosis/monitoring, genetics/biomarkers, cardiac catheterization, echocardiography, cardiac magnetic resonance/chest computed tomography, associated forms of PH, intensive care unit/lung transplantation, and treatment of pediatric PH. For the first time, a set of specific recommendations on the management of PH in middle- and low-income regions was developed. Taken together, these executive, up-to-date guidelines provide a specific, comprehensive, detailed but practical framework for the optimal clinical care of children and young adults with PH.
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Pulmonary hypertension (PH) and associated pulmonary vascular disease (PVD) are characterized by pulmonary vascular remodeling leading to elevated pulmonary arterial pressure and, over time, right ventricular (RV) dysfunction, underfilling/compression of the left ventricle, and terminal heart failure.[1−3] PH-associated mortality has been decreasing over the last 2 decades in children[4] and adults,[5] likely because of increased awareness of this condition and its multiple etiologies, more accurate diagnosis, better risk stratification, and early initiation of combination pharmacotherapy.[3,5−7] Nevertheless, transplant-free survival of children and adults with idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), and other forms of World Health Organization (WHO) Group 1 PH, such as Eisenmenger syndrome and persistent pulmonary arterial hypertension (PAH) after repair of congenital heart disease (CHD) (PAH-CHD) remains poor.[3,4,8,9] Although there is currently no cure for PAH, both the established and experimental therapies aim to stop or even reverse disease progression, thereby relieving the significant morbidity and mortality and improving the patients' quality of life.

Rationale for the 2019 updated consensus on pediatric PH

The 2015 European Society of Cardiology (ESC) and European Respiratory Society guidelines on the diagnosis and treatment of PH includes comprehensive recommendations on the diagnosis and treatment of PH but mainly focuses on clinical care in adults.[10] Both a new definition and an expanded classification of PH were developed at the World Symposium on PH (WSPH, Nice, 2018)[11,12] (Box 1 and 2; Supplementary Tables S1, S2, and S3, available online at www.jhltonline.org). The unique features of pediatric PH were recognized for the first time at the 2013 WSPH, resulting in a dedicated short document on pediatric PH[13] that was recently updated.[12] Based on our previous expert consensus recommendations in 2016,[14] we deliver updated, comprehensive, practical guidelines for healthcare providers addressing the specifics of PH and PVD in children and young adults.

Objectives of the 2019 Consensus Statement of the European Pediatric PVD Network (EPPVDN)

In 2016, the EPPVDN published a multipaper consensus statement that contains practical recommendations for health care providers treating children and adolescents with different forms of PH.[14]

The objectives of our 2019 guidelines on pediatric PH are the following:

1. To briefly discuss the most recent changes to the classification and definition of PH and its subtypes (World Symposium on PH in Nice 2018);[11,12]
2. To outline clinical study results and their limitations;
3. To provide graded, evidence-based, and expert-based recommendations for optimal diagnosis and treatment of infants, children, and young adults with PH (including CHD/Eisenmenger and single ventricle physiology/Fontan), according to the grading system provided by the American Heart Association and ESC;
4. To address features of the disease and its management that are specific to pediatric PH;

5. To define the multiple gaps in our knowledge on pediatric PH; and
6. To briefly discuss emerging PH therapies (safety and efficacy).

Methodology

Goals and composition of the EPPVDN's executive writing group (EWG)

The EPPVDN is a registered non-profit organization. The network strives to define and develop effective, innovative diagnostic methods and treatment options for all forms of pediatric PH and associated heart failure. The EWG members were recruited from Austria, Belgium, Germany, Finland, France, India, Italy, Pakistan, Sweden, Switzerland, the United Kingdom, and the United States of America. The EWG consisted of 22 pediatricians (with expertise and board certifications in pediatric cardiology, critical care, pulmonology, neonatology, sports medicine, and/or genetics), 7 doctors with subspecialty certifications for adults with CHD (3 adult cardiology, 4 pediatric cardiology), 1 adult pulmonologist, and 1 thoracic transplant surgeon.

Special features of the 2019 guidelines on pediatric PH

Previously, we followed a novel approach to develop 10 individual papers sorted by clinical topic, including "diagnosis/monitoring"[6], "treatment"[7], and an "executive summary"[14], in a special issue on pediatric pulmonary hypertension (https://heart.bmj.com/content/102/Suppl_2). In these guidelines, status after the WSPH 2018 meeting, we updated and expanded the 2016 executive summary to develop the 2019 EPPVDN guidelines. The following disease-specific, complex, and common patient groups are addressed separately: (1) PH associated with CHD, including recommendations for both children and young adults with PAH-CHD; and (2) persistent PH of the newborn (PPHN) and PH associated with bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) in infancy. The 2019 updated EPPVDN guidelines also give detailed recommendations on the treatment of acute PH in the intensive care unit, including extracorporeal membrane oxygenation and lung transplantation, and comprehensive recommendations on mid- to long-term treatment of PH in inpatient and outpatient settings, including pharmacotherapy, catheter interventions, and surgery. Moreover, for the first time, we highlight the challenges and special aspects of diagnostics and treatment of PH in middle to low income regions (MLIRs). This consensus document has been endorsed by the Association for European Pediatric and Congenital Cardiology (AEPC), the European Society for Pediatric Research (ESPR), and the International Society of Heart and Lung Transplantation (ISHLT).

Literature search

Searches of the PubMed/MEDLINE bibliographic database were conducted for the time period 1990−2018. Clinical studies/trials, guidelines, consensus statements, and reviews including pediatric data and/or adults with CHD were searched using the terms "pulmonary hypertension" and up to 10 other keywords. The primary focus of this manuscript is on group 1 PH, according to the WSPH in Nice, 2018.[11]

Class of recommendation (COR) and level of evidence (LOE)

The COR and LOE grading was based on pediatric PH study data, adult PAH studies enrolling >10% children, or studies on children

Table 1 COR as Currently Proposed by the ESC and the AHA

Class of recommendation	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/ is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well Established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

AHA, American Heart Association; COR, class of recommendation; ESC European Society of Cardiology.

The color coding was used throughout the 2019 Updated Guidelines on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension—The European Pediatric Pulmonary Vascular Disease Network.

Table 2 LOE as Currently Proposed by the ESC and the AHA

Level of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

AHA, American Heart Association; ESC European Society of Cardiology; LOE, level of evidence.

The color coding was used throughout the 2019 Updated Guidelines on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension—The European Pediatric Pulmonary Vascular Disease Network.

Box 1. Definitions

Pulmonary Hypertension (PH), according to the recent WSPH (Nice, 2018)
mPAP > 20 mm Hg in children >3 months of age at sea level

Pre-capillary PH (e.g., PAH)
mPAP > 20 mm Hg
PAWP or LVEDP ≤ 15 mm Hg[a]
PVR index ≥ 3 WU × m^2 (PVR ≥ 3 WU in adults)
Diastolic TPG (DPG) ≥ 7 mm Hg (adjunct criterion)

Isolated post-capillary PH (Ipc-PH) in adults (e.g., predominantly diastolic LV dysfunction [HFpEF][a])
mPAP > 20 mm Hg
PAWP or LVEDP > 15 mm Hg
PVR index < 3 WU × m^2 (PVR <3 WU in adults)
Diastolic TPG (DPG) < 7 mm Hg (adjunct criterion)

Combination of pre-capillary and post-capillary PH (Cpc-PH) in adults[a]
mPAP > 20 mm Hg
PAWP or LVEDP > 15 mm Hg
PVR ≥3 WU (PVR index ≥ 3 WU × m^2 in children)

Pulmonary Arterial Hypertension (PAH)
mPAP > 20 mm Hg
PAWP or LVEDP ≤ 15 mm Hg[a]
PVR index ≥ 3 WU × m^2, plus criteria for group 1 PH

Idiopathic PAH (IPAH)
PAH with no underlying disease known to be associated with PAH

Heritable PAH (HPAH)
PAH with no known underlying disease but with positive family history or positive genetic testing of the index patient

Eisenmenger syndrome (ES)
Patient with longstanding pulmonary hypertension, suprasystemic PVR and PAP, and accordingly, right-to-left cardiovascular shunting with systemic hypoxemia (e.g., unrepaired VSD or PDA).

Pulmonary Hypertensive Vascular Disease (PHVD)#[b]
For biventricular circulations: mPAP > 20 mm Hg and PVR index ≥ 3 WU × m^2
For circulations with cavopulmonary anastomosis (e.g., Fontan physiology):
Mean TPG > 6 mm Hg (calculate mPAP minus mLAP or PAWP) or PVR index > 3 WU × m^2

Box 1. The classification of PH according to the WSPH (Nice, 2018)[11] and the classification of pediatric PHVD[15] can be found in Supplementary Tables S1 and S2, respectively (available online). Details on hemodynamic definitions, invasive measures, and clinical implications are given in Supplementary Table S3 online. Detailed hemodynamic definitions of PH (e.g., value of the diastolic TPG) can be found in the 2015 ESC/ERS guidelines,[10] Hansmann (2017)[3] and Apitz et al. (2016)[16] It should be noted that even mildly elevated mPAP values (20—24 mm Hg, prognostic threshold 17 mm Hg) are independent predictors of poor survival in adults with PH (Douschan et al., 2018).[17] In adults, PVR is usually not indexed to BSA.
[a]In many instances, it is useful to measure the PAWP simultaneously with LVEDP.
[b]PVRI-Panama classification of pediatric PHVD, 2011 mPAP ≥ 25mm Hg used to define PH
BSA, body surface area; Cpc-PH, combination of pre-capillary and post-capillary pulmonary hypertension; DPG, diastolic pulmonary gradient; ERS, European Respiratory Society ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; Ipc-PH, isolated post-capillary pulmonary hypertension; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; mLAP, mean left atrial pressure; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PVR, pulmonary vascular resistance; TPG, transpulmonary pressure gradient; VSD, ventricular septal defect; WSPH, World Symposium on Pulmonary Hypertension; WU, Wood units.

Box 2. What is new in the 2019 Updated EPPVDN Consensus Statement on Pediatric PH?

1. The WSPH 2018 modified the definition and classification of PH presented in the 2015 ESC/ERS Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension.[10] In particular, the lower limit of normal mPAP was decreased from 24 to 20 mm Hg.[11] Even mildly elevated mPAP values (20–24 mm Hg, prognostic threshold 17 mm Hg) were recently found to be independent predictors of poor survival in adults with PH.[17] For consistency, this new definition of PH was also used in the pediatric WSPH 2018 document[12] and our 2019 EPPVDN consensus statement, although the cut-off mPAP > 20 mm Hg remains arbitrary because no according prognostic pediatric data are available.
2. As in adults, a sub-group of children with IPAH can be identified who are positive responders to AVT and would now be classified as "PAH long-term responders to CCBs" according to the WSPH 2018 (Group 1.5 PH).[11] AVT is estimated to be positive in approximately 15–30% of children with IPAH, depending on the AVT criteria applied (Sitbon, 15%; modified Barst/pediatric REVEAL, 30%). Because only half of the adult responders have a long-term hemodynamic and clinical improvement on CCB therapy, close long-term follow-up is required, and combination therapy may be warranted once CCB monotherapy becomes partly inefficient.
3. PAH and PVOD/PCH are now considered a spectrum of PVDs rather than two clearly distinct entities.[11] According to the WSPH 2018, Group 1.6 PH is now called PAH with overt features of venous/capillary involvement (PVOD/PCH).[11] The prevalence for IPAH is 2.1–4.4 cases per million children,[12] but several-fold higher for PAH-CHD. PVOD/PCH was diagnosed in only 0.7%–2% of PAH cases in European pediatric registries,[12] and thus appears to be very rare.
4. Diagnostic methods and variables and their application in pediatric PH have been updated. In particular, the EPPVDN evaluated new echocardiographic surrogate variables for its use in pediatric PH (normal reference values by age and gender available). The diagnostic algorithm is shown in Figure 1.
5. The EPPVDN updated the table on pediatric determinants of risk according to new clinical pediatric PH data (Figure 2). A new Risk Score Sheet for Pediatric PH (Hansmann G et al., EPPVDN, 2019) has also been developed and may be used for risk stratification (Supplementary Figure S1 online).
6. New treatment algorithms (Figures 3 and 4) are presented, in addition to pharmacotherapy (Supplementary Tables S4 and S5 online) and drug–drug interactions (Supplementary Table S6 online). Furthermore, new treatment options for pediatric PH and/or PAH-CHD are mentioned, based on the first pediatric experience with off-label, compassionate use of PAH medications (i.e., selexipag and riociguat; Supplementary Table S5 online).
7. Entirely new recommendations on challenges and special aspects in the diagnostics and treatment of PH in middle to low income regions (MLIRs) are given.

AVT, acute vasoreactivity testing; CCB, calcium-channel blocker; CHD, congenital heart disease; EPPVDN, European Pediatric Pulmonary Vascular Disease Network; ERS, European Respiratory Society; ESC, European Society of Cardiology; IPAH, idiopathic pulmonary arterial hypertension; middle to low income region; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVOD, pulmonary veno-occlusive disease; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; WSPH, World Symposium on Pulmonary Hypertension.

and adults with PAH-CHD. Details on the ESC/American Heart Association grading system for COR (Table 1) and LOE (Table 2), as well as the voting, peer review, and endorsement process, can be found in the Supplementary Material online. The supplement also includes additional text, figures, tables, and the supplementary references per section (ref. S3-1 to S12-26), as listed in numerical order in the graded recommendations (Tables 3–12). Importantly, healthcare providers must adhere to the medication labeling and follow future drug recommendations/warnings potentially published by the European Medicines Agency and the US Food and Drug Administration when applying these recommendations in clinical practice.

Summary of graded recommendations by clinical topic

Diagnostics, monitoring, and outpatient care in children or young adults with suspected PH

A diagnostic algorithm for a child or young adult with suspected PH can be found in Figure 1. Here, we make recommendations on established and newly identified diagnostic and monitoring variables, tools, and procedures in pediatric PH (Table 3). A new EPPVDN pediatric PH risk score sheet can be found in the Supplementary Material (Supplementary Figure S1). Further details and the technical and methodologic limitations of the diagnostic tools are discussed elsewhere.[6]

Transthoracic echocardiography in children with suspected PH

We focus our recommendations on newly developed key transthoracic echocardiography variables with according normal reference values including RV outflow tract size and flow, right atrial function, and pulmonary arterial acceleration time (Table 4). Special attention is given to relevant ventricular–ventricular interaction variables that are used to determine pressure, myocardial contractility, flow, and systolic and diastolic function of both ventricles. A detailed

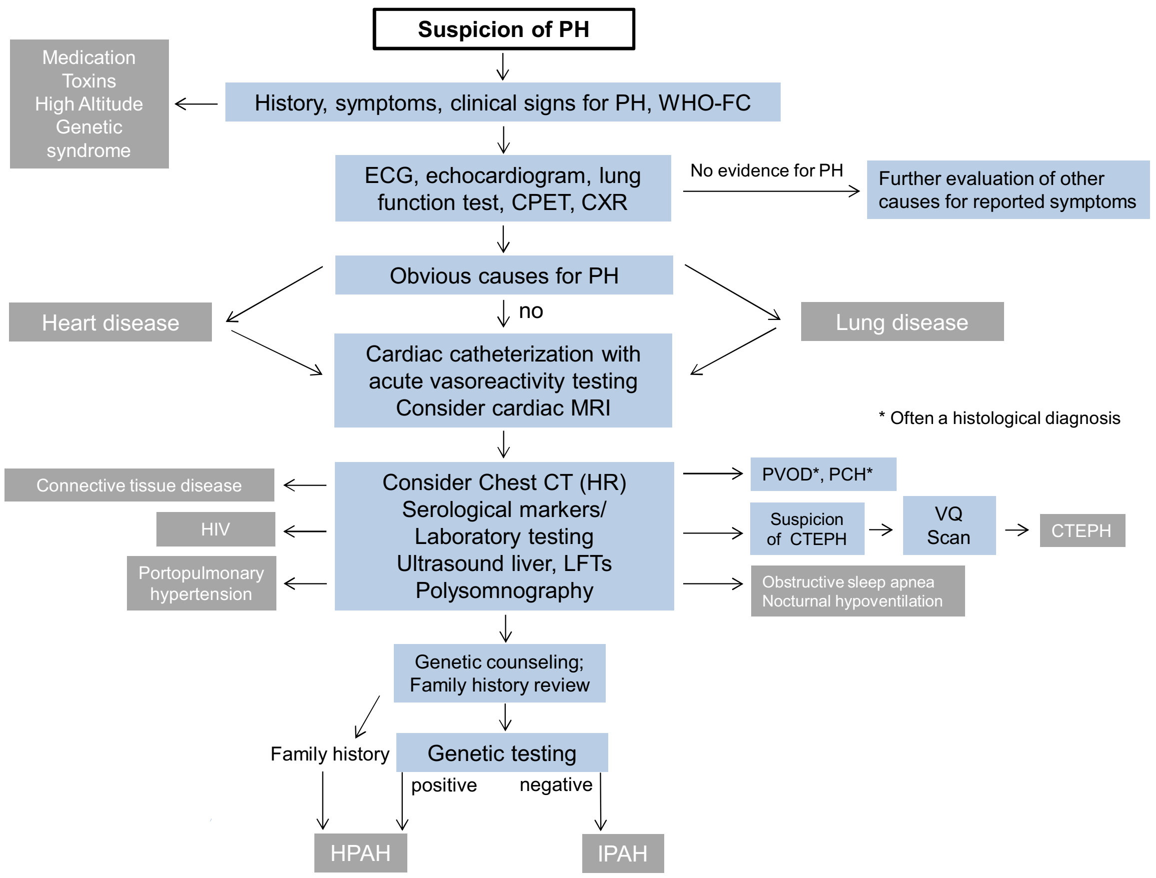

Figure 1 **Diagnostic algorithm for a child or young adult with suspected PH.** Screening for pediatric PH is performed by ECG and echocardiography. If these investigations suggest the presence of PH/PHVD, chest X-ray and/or chest CT should be considered, followed by additional investigations. If PH/PHVD is severe, and the patient presents severely ill in overt heart failure and/or pulmonary vascular crisis, cardiac catheterization may be postponed and pharmacotherapy including intravenous prostanoids started immediately. CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CXR, chest X-ray; ECG, electrocardiogram; FC, functional class; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; HR, high resolution; IPAH, idiopathic pulmonary arterial hypertension; LFT, liver function test; MRI, magnetic resonance imaging; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PVOD, pulmonary veno-occlusive disease; VQ, ventilation/perfusion; WHO, World Health Organization. Modified from Lammers et al., 2016.[6]

echocardiography protocol and the technical and methodologic limitations are discussed elsewhere.[18]

Hemodynamic assessment and acute pulmonary vasoreactivity testing (AVT) in the evaluation of children with PH/PVD (cardiac catheterization)

The hemodynamic definition of PH, including sub-types of this heterogeneous condition, and its classification have been revised and updated recently.[11] The recommendations of the EPPVDN (2019) include these recent changes and continue to focus on the clinical implication of accurate hemodynamic assessment of children with PH/PVD (Table 5). Newly derived data from pediatric studies and registries have been screened and are enclosed to support evidence-based performance of invasive hemodynamic assessment and AVT in children with PH. A detailed discussion on diagnostic cardiac catheterization in pediatric PH can be found elsewhere.[16]

Use of cardiac magnetic resonance (CMR) and computed tomography (CT) in children with suspected or confirmed PH

We introduce newly developed key variables such as the CT-derived ratio of mean pulmonary artery to ascending aorta inner diameter that, when increased, raises the suspicion for pediatric PH (Table 6). Special attention is also given to CMR assessment of biventricular systolic function that may help to detect pathophysiologic processes associated with severe PH. Detailed protocols and the technical limitations of CT and CMR non-invasive imaging are discussed elsewhere.[19]

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
Normal (height, BMI)	Growth	Failure to thrive
I, II	WHO functional class	III, IV
Minimally elevated for age or not elevated	Serum NT-proBNP	Greatly elevated for age >1200 pg/mL (>1yr old) Rising NT-proBNP level
Minimal RA/RV enlargement No RV systolic dysfunction RV/LV e.s. ratio < 1 (PSAX) TAPSE normal (z > -2) S/D ratio <1.0 (TR jet) PAAT > 100 ms (>1yr old)	Echocardiography, CMR	Severe RA/RV enlargement RV systolic dysfunction RV/LV e.s. ratio >1.5 (PSAX) TAPSE ↓↓ (z < -3) S/D ratio >1.4 (TR jet) PAAT <70 ms (>1yr old) Pericardial effusion
CI >3.0 l/min/m² mRAP <10 mm Hg mPAP/mSAP <0.5 Acute vasoreactivity +	Invasive Hemodynamics	CI <2.5l/min/m² mRAP >15 mm Hg mPAP/mSAP >0.75 PVRi >15 WU · m²

Figure 2 **Determinants of risk in pediatric PH and suspected PHVD.** Variables are listed that distinguish between lower risk and higher risk, while the intermediate risk group is broad and not specifically defined. Overall, these determinants have only level of evidence C because of sparse or lacking pediatric data. Healthcare providers may include here PVR/SVR ratio, the 6 minute walk distance, and VO_{2max} obtained during cardiopulmonary exercise testing as risk variables; however, it is unclear where exactly the cut-off values should be set. One must also note that most of these variables have been validated mostly for IPAH, and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk. See also supplementary Figure S1 for the EPPVDN risk score sheet (PH risk stratification). BMI, body mass index; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiovascular magnetic resonance imaging; e.s., end-systolic; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; mSAP, mean systemic artery pressure; NT-proBNP, N terminal pro BNP; PAAT, pulmonary artery acceleration time by transthoracic Doppler echocardiography; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PSAX, parasternal short axis view by transthoracic echocardiography; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RA, right atrium; RV, right ventricle; S/D ratio, systolic/diastolic duration ratio by Doppler echocardiography; SVR, systemic vascular resistance; SVRi, systemic vascular resistance index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VO_{2max}, maximum rate of oxygen consumption; WHO, world health organization; WU, Wood unit. Modified from Hansmann et al., 2016.[14]

Use of genetic counseling and testing and biomarkers in children with PH

We provide detailed recommendations on genetic testing in pediatric patients with PH and family members. In addition, we give recommendations for the determination of blood biomarkers at diagnosis and follow up (Table 7).[6] An algorithm on genetic counseling and testing for a child with IPAH or HPAH and his/her family members is presented in Supplementary Figure S2 online. A general discussion on genetic counseling/testing and biomarkers in pediatric PAH can be found elsewhere.[20] The WSPH 2018 task force on genetics and genomics in PH estimated that approximately 25%–30% of patients diagnosed with IPAH have an underlying Mendelian genetic cause for their condition and should more accurately be classified as HPAH (with an identified pathogenic gene variant).[21] Down syndrome-related PH varies in terms of etiology and severity, and—in the absence of CHD (Group 1 or Group 2)—should be classified as Group 3 PH (Supplementary Tables S1 and S10 online).[12]

Evaluation and management of PH in children and young adults with CHD (PAH-CHD and pulmonary hypertensive vascular disease [PHVD]–CHD)

We focus our recommendations on the operability and treatment of children with simple (Figure 3) or complex CHD (Table 8). Special attention is given to a new *treat-to-close (treat-and-repair) approach* in highly selected patients with a pre- or post-tricuspid shunt from the grey zone (pulmonary vascular resistance index, 6–8 WU $\cdot m^2$), that is, pre-

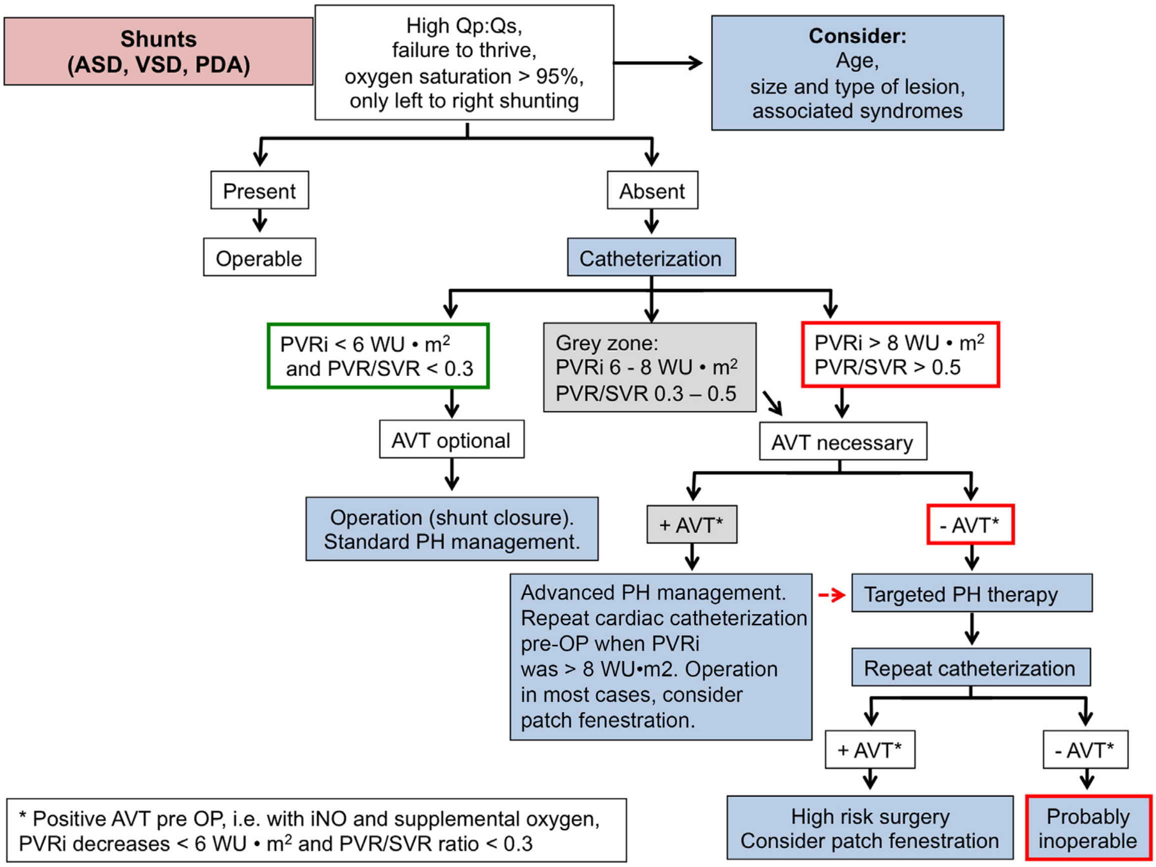

Figure 3 **Algorithm for the management of patients with CHD associated with PAH/PHVD and congenital shunt lesions.** The indication for invasive diagnostics and eligibility for surgery/operability by comprehensive right and left heart catheterization includes basic evaluation and AVT, the latter especially in the gray zone of forecast uncertainty. Red frames indicate likely inoperable. Green frames indicate operability (pursue complete shunt closure). Of note: This algorithm does not cover the difficult treatment of children and young adults with isolated or predominantly post-capillary PH because of post-capillary obstructive lesions, for example, in the setting of pulmonary vein stenosis, mitral stenosis or other small left-sided structures (Supplementary Table S8 online), or cardiomyopathy with elevated left ventricular end-diastolic filling pressures. AVT, acute vasoreactivity testing; ASD, atrial septal defect; CHD, congenital heart disease; iNO, inhaled nitric oxide; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; pre-OP, preoperatively; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qp, pulmonary blood flow; Qs, systemic blood flow; SVR, systemic vascular resistance; VSD, ventricular septal defect; WU, Wood unit. Modified from Lopes and Barst and the Pulmonary Vascular Research Institute PAH-CHD taskforce (Pulmonary Vascular Research Institute website; published on September 26, 2013) and Kozlik-Feldmann et al., 2016.[22]

operative mono- or dual PAH-targeted pharmacotherapy (Figure 3). When PAH persists after cardiovascular shunt closure, patients with repaired CHD may be treated with a phosphodiesterase-5 inhibitor and/or endothelin receptor antagonist (Supplementary Tables S4 and S5 online). Complex heart diseases specific for the pediatric age group that are associated with congenital anomalies of the pulmonary vasculature, such as segmental PH, single ventricle physiology, and the scimitar syndrome, are listed in Supplementary Table S7 online and often require an individualized, multidisciplinary approach. An individualized approach is also needed for congenital post-capillary obstructive lesions, such as pulmonary vein stenosis and small left-sided cardiac structures (Supplementary Table S8 online), as well as for restrictive cardiomyopathy with isolated post-capillary PH or combined pre- and post-capillary PH (Supplementary Table S3 online). Further details on PH-CHD in children and young adults are discussed elsewhere.[3,22–24]

Supportive measures and pharmacotherapy in PPHN and PH associated with bronchopulmonary displasia (BPD)/neonatal chronic lung disease (CLD)

In the following section, we provide practical recommendations on the treatment of infants with PH, including PPHN, BPD-PH, and neonatal CLD. In addition, we focus on supportive measures, monitoring, and diagnostics of infants with BPD-PH and PPHN (Table 9). A detailed discussion of and algorithms for the clinical management of PPHN

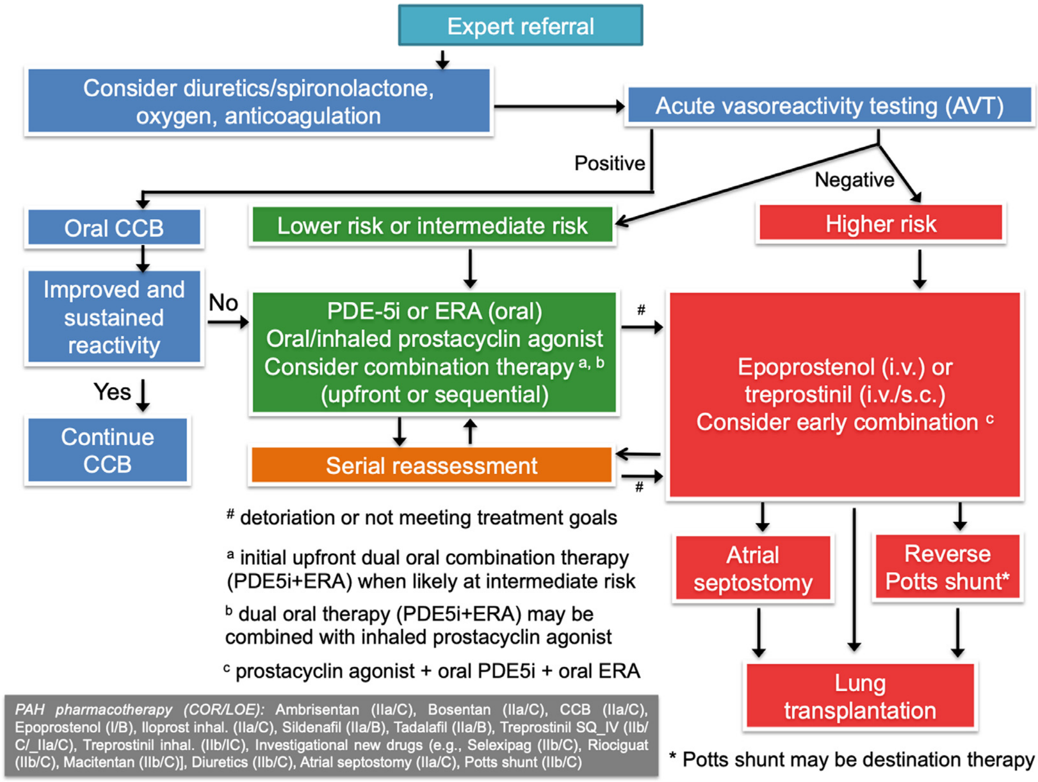

Figure 4 **Treatment algorithm for pediatric PAH.** This algorithm applies to IPAH and HPAH (previously called familial PAH). Solid clinical data on the therapy of other forms of PH are limited, but the algorithm may apply to adult patients with DPAH. Initial monotherapy may be considered only when patient is at low risk (residual role for monotherapy). Monotherapy (e.g., with PDE-5i) in PAH-CHD after shunt closure and monotherapy (mostly with PDE-5i) in BPD-PH and CLD-PH is commonly used (residual role for monotherapy). We recommend initial upfront dual oral combination therapy (PDE-5i + ERA) when the patient is likely at intermediate risk. Dual oral therapy may be combined with inhaled, intravenous, or subcutaneous prostacyclin agonist (prostacyclin analogue), depending on risk stratification and clinical condition. Patients should be referred to a lung transplantation center for LuTx evaluation when they remain in an intermediate- or high-risk category despite maximal PAH therapy. In experienced centers, the 1-year survival rates after LuTx now exceed 90%. A pre-transplant rehabilitation program may be considered. Aside from sildenafil and bosentan (>1 year of age), all other agents are considered off-label drugs in children with PH in Europe. Sildenafil dosing recommendations should follow EMA-approved dosing for children. Bosentan received the following dual grading: COR I, LOE B for children with PAH and ES, and COR IIa, LOE C for children with PAH without ES. AVT, acute vasoreactivity testing; CCB, calcium channel blocker; COR, class of recommendation; DPAH, drug-induced pulmonary arterial hypertension; EMA, European Medicines Agency; ERA, endothelin receptor antagonist; ES, Eisenmenger syndrome; HPAH, heritable pulmonary arterial hypertension; inh., inhalation; IPAH, idiopathic pulmonary arterial hypertension; i.v., intravenously; LOE, level of evidence; PDE-5i, phosphodiesterase 5 inhibitor; s.c., subcutaneously.

(Supplementary Table S9 online) and BPD- and CLD-PH (Supplementary Table S10 online) can be found elsewhere.[25]

Therapy of acute PH in the pediatric intensive care unit: Pharmacotherapy and mechanical circulatory support

Management of children with PH can be be extremely challenging in the critical care setting. Children with pre-existing IPAH (acute-on-chronic) and those with PAH-CHD (e.g., peri-operatively) especially are high-risk populations. Basic management of critically ill patients with PH includes application of oxygen and treatment of triggering or aggravating factors such as acidosis, agitation, pain, volume overload or dehydration, arrhythmia, anemia, and infection. Targeted therapy to decrease the RV pressure afterload (Table 10) is accompanied by pharmacotherapy to increase myocardial perfusion and to counteract right-to-left interventricular septal shift.

Treatment of pediatric PH

PHVD and associated heart failure is complex, and the selection of appropriate therapies remains difficult in children and young adults. The so-called PAH-specific medications currently approved for therapy of adults with PAH target 3 major pathways (endothelin, nitric oxide, and prostacyclin). Moreover, some PH centers may use off-label drugs for compassionate use in selected cases. Pediatric PAH therapy is largely based on expert experience

Table 3 Recommendations on the Diagnostics, Monitoring, and Outpatient Care in Children with PH

Recommendations	COR	LOE
Children with suspected or confirmed PH should be evaluated and treated in specialized pediatric centers.	I	C
The initial evaluation should include a comprehensive medical history, physical examination, assignment to a functional class, and assessment of cardiac function (ECG and echocardiogram). This should be followed by further diagnostic testing to delineate the PH etiology—ideally before the initiation of therapy. (S3-1—S3-5)	I	B
A CXR is recommended at baseline with acceptable risk/radiation exposure.	I	C
Regular CXRs at follow up visits are not indicated, unless there is a clinical reason (S3-6, S3-7).	III no benefit	C
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. (S3-1—S3-5)	I	B
An ECG can be beneficial to detect right ventricular hypertrophy or arrhythmia. However, it cannot serve as a screening tool in isolation because of limited sensitivity and specificity. (S3-3,S3-4)	IIa	C
Further imaging is recommended to exclude underlying parenchymal lung disease, PVOD, CTEPH, and anatomical obstructions, which may be beyond what can be diagnosed by transthoracic echocardiography. (S3-7—S3-10)	I	C
If a definite diagnosis is still pending despite other imaging modalities (cardiac catheterization, HR-chest CT with angiography), a VQ scan can be useful for patients with high suspicion for CTEPH. (S3-11,S3-12)	IIa	C
If PoPH is suspected (i.e., ascites, splenomegaly, echocardiography, abdominal ultrasound), cardiac catheterization and additional non-invasive imaging should be considered. (S3-13,S3-14)	IIa	C
A sleep study (polysomnography) should be performed in patients with PH at risk for sleep-disordered breathing, especially patients with trisomy 21, systemic diseases, other syndromes, patients with small upper airways, and patients with significant daytime sleepiness. (S3-15,S3-16)	I	B
Serial CPET and 6MWT should include pulse oximetry and stress ECG during CPET and are recommended to assess exercise tolerance, arrhythmia risk, and response to therapy, and to estimate prognosis in children with PH capable of performing such studies. (S3-17,S3-18)	I	B
Blood gas analysis in pediatric patients with PH can be useful at rest, at ventilatory threshold, and at maximal exercise during CPET. (S3-19)	IIa	C
A lung function test (advanced: body plethysmography) and diffusion capacity measurement (DLCO) are recommended at the time of diagnosis to rule out any coexisting airway/lung disease (obstructive, restrictive, and combined).	I	C
Because certain drugs (e.g., inhaled iloprost) may cause bronchospasm, a lung function test is reasonable before the start of any inhalation PH therapy. (S3-20)	IIa	C
In children with end-stage PH, timely referral to a transplant center is beneficial, if lung transplantation represents an option for the individual patient. (S3-21)	I	C
Children with PH undergoing procedures requiring sedation or general anesthesia should be cared for by a cardiac anesthesiologist or cardiac intensivist with sufficient pediatric PH experience. The surgical benefit of any elective or plastic surgery should be carefully evaluated against the associated anesthetic risk. (S3-22)	I	C
Female adolescents with PH should undergo timely counseling regarding the significant maternal and fetal pregnancy risks and options for secure contraception. (S3-23,S3-24)	I	B
Children with PH in the higher-risk category should not participate in competitive sports. Participation in light exercise is beneficial but should only be undertaken after medical consultation and detailed serial assessment including exercise testing.	I	C
Children with mild to moderate PH should engage in regular light-to-moderate aerobic activity. They should be allowed to self-limit their activities as required but avoid strenuous and isometric exercise, dehydration, and exercise at moderate (1500—2500 meters) or high (>2500 meters) altitude.	I	C
Children with PH may fly on commercial airplanes in a stable and compensated condition after consultation with a pediatric PH expert who will advise on supplemental oxygen and maximum flight duration. Travel to high altitude (>2500 meters) may not be advisable. (S3-25)	IIb	C
It is useful for children with PH to undergo all recommended routine vaccinations (including pneumococcal), RSV immunoprophylaxis (<2 years of age), and influenza vaccinations to prevent any deterioration because of avoidable infections, if no other contraindications exist. (S3-26)	I	C
Serial measurements of serum NT-proBNP concentration are indicated as changes in NT-proBNP may reflect ventricular impairment. (S3-27)	I	C
Antibiotic prophylaxis for the prevention of sub-acute bacterial endocarditis is reserved for special patient sub-groups (e.g., cyanotic patients including patients with atrioseptostomy and Potts shunt or patients with residual cardiovascular shunt). (S3-28)	I	C
Genetic testing should be discussed with the patient and family and recommended in view of the increasing knowledge of the correlation between phenotype and mutations in single genes, for example, *BMPR2*. Positive testing may justify an early escalation of therapy and placement of a patient into a higher-risk category in the absence of other high-risk criteria. (S3-29)	I	C
Accelerometry (wrist or hip device) may be considered to monitor exercise capacity and well-being in children with PH. (S3-30)	IIb	C

6MWT, six-minute walk test; COR, class of recommendation; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; CXR, chest X-ray; DLCO, diffusing capacity of the lungs for carbon monoxide; HR-chest CT, high resolution chest computed tomography; ECG, electrocardiography; LOE, level of evidence; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PoPH, portopulmonary hypertension; PVD, pulmonary vascular disease; PVOD, pulmonary veno-occlusive disease; RSV, respiratory syncytial virus; VQ, ventilation-perfusion.

The above recommendations relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and were based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S3-1 to S3-30) on the above topic can be found in the Supplementary Material online. See also the diagnostic algorithm (Figure 1), determinants of risk (Figure 2), algorithm on PAH-congenital heart disease (Figure 3), classifications (Supplementary Tables S1 and S2 online) and definitions (Supplementary Table S3 online). Specific recommendations on specific diagnostic tools are given in Tables 4—6.

Table 4 Recommendations on Transthoracic Echocardiography (TTE) in Children with Suspected PH or Confirmed

Recommendations	COR	LOE
Following the initial diagnostic evaluation for PH, TTE should be performed in 3- to 6-month intervals or earlier when clinical worsening is suspected.	I	C
An echocardiographic study should include an assessment of the following TTE variables (•): • Estimation of systolic PAP (in the absence of RVOT obstruction), by estimating RVSP through the measurement of TR velocity jet (S4-1,S4-2)	I	B
• Estimation of mean PAP and end-diastolic PAP through CW-Doppler of the pulmonary regurgitation jet (S4-3)	IIa	C
• RV longitudinal systolic function (TAPSE, FAC) (S4-4—S4-6)	I	B
• RV strain and strain measurements (S4-7—S4-9)	IIa	B
• RV size and function assessment with 3D echocardiography (S4-10,S4-11)	IIb	B
• RV base/apex ratio in determination of pediatric PH (S4-12)	IIb	B
• RV systolic to diastolic duration ratio (CW-Doppler, TR jet) (S4-13,S4-14)	IIb	B
• Tissue Doppler velocities (LV, septal, RV) (S4-15—S4-17)	IIa	B
• RVOT size enlargement (S4-18)	IIb	B
• RVOT VTI and TRV/RVOT VTI ratio determination (S4-18,S4-19)	IIa	B
• PAAT determination is useful in children with suspected/confirmed PH. (S4-1,S4-20—S4-22)	I	B
• Determination of the left heart variables (i) end-systolic LV eccentricity index, (ii) end-systolic RV/LV diameter ratio, and (iii) classical indicators of diastolic LV dysfunction (see below), all of which are impacted by ventricular—ventricular interaction, can be useful in pediatric PH patients. (S4-17,S4-23—S4-26)	IIa	B
• RA and RV size (2-dimensional area, FAC) enlargement (S4-27—S4-30)	IIa	B
• RA function (RA deformation, RA volume) (S4-31,S4-32)	IIb	B
• RV and LV diastolic function parameters (reduced mitral E velocity and inflow duration, mitral E′ and E′/A′, septal E′ and A′, increased mitral E deceleration time, LV isovolumic relaxation time, mitral E/E′) (S4-16,S4-17,S4-33—S4-35)	IIa	B
TTE cannot establish the definite diagnosis of PH or determine the WHO PH group.	I	C
PH diagnosed by TTE should be confirmed by cardiac catheterization before initiation of targeted PH pharmacotherapy (except in infants with PPHN or BPD-PH or too high risk). (S4-1,S4-35)	I	C
Expert TTE in pediatric PH follows a multiparametric approach and should not rely on a single echocardiographic parameter.	I	C

3D, three dimensional; BPD, bronchopulmonary dysplasia; COR, class of recommendation; CW, continuous wave; FAC, fractional area change; LOE, level of evidence; LV, left ventricle; PAAT, pulmonary arterial acceleration time; PAP, pulmonary arterial pressure; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PH, pulmonary hypertension; PE, pericardial effusion; PPHN, persistent pulmonary hypertension of the newborn; RA, right atrium; RV, right ventricle; RVOT, right ventricle outflow tract; RVSP, right ventricle systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; TR, tricuspid regurgitation; VTI, velocity time integral; WHO, World Health Organization.

The above recommendations relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and were based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S4-1 to S4-35) on the above sub-topic can be found in the Supplementary Material online.

and trial data from adult studies; however, the first randomized pediatric PAH trials have been conducted recently. Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (PVOD/PCH) is now considered within the spectrum of PAH, characterized by very pronounced venous/capillary involvement (Box 1), and as such is a condition that is associated with a particularly poor prognosis, very limited response to PAH therapy, and the risk of pulmonary edema with vasodilator therapy.

Here, we make recommendations (Table 11) on early combination therapy (double or triple) in PAH patients in WHO functional class II—IV, including those with inadequate response to the initial pharmacotherapy (Figure 4; Supplementary Tables S4 and S5). In those patients with progressive, severe PAH and inadequate response to therapy, advances in drug development and both interventional and surgical procedures provide strategies to prevent, reverse, or ameliorate all, RV pressure overload, left ventricular compression/underfilling, and ultimately end-stage heart failure.

Diagnosis and management of PH in middle to low income regions (MLIRs)

In this section, we focus on diagnosis and management of PH in MLIRs where PH prevalence is high and etiology is broad. Special attention is given to the diagnosis of left heart disease (i.e., rheumatic heart disease), acquired lung diseases (i.e., tuberculosis), infections such as HIV and schistosomiasis, and unrepaired CHD. Additionally, we discuss operability in late-presenting patients with CHD and the role of phlebotomy in patients with Eisenmenger (Table 12). Recommendations covered in other sections (chest X-ray, electrocardiogram, pulse oximetry in 6-minute walk test, phlebotomy and anticoagulation in Eisenmenger patients, pregnancy counseling, and antibiotic prophylaxis for subacute bacterial endocarditis) are not mentioned in this table. So far, only very few registries exist worldwide that can provide useful information on PH in MLIRs (Supplementary Figure S3 online).

Table 5 Recommendations on Invasive Hemodynamic Assessment and AVT in the Evaluation of Children with PH/PVD

Recommendations	COR	LOE
Cardiac catheterization is indicated in all pediatric patients with PH to confirm diagnosis and to determine severity, and anytime when PH-specific drug therapy is considered. Exceptions may apply to infants with PH and low body weight (<2–5 kg), in which case cardiac catheterization may be postponed or even omitted. Classical PPHN is a contraindication for cardiac catheterization. (S5-1–S5-5)	I	C
Initial cardiac catheterization should include right and left heart catheterization to establish the diagnosis (not only RHC), if there is no contraindication. (S5-3–S5-5)	I	C
Cardiac catheterization can be postponed in acutely presenting, critically ill patients requiring immediate initiation of therapy but not omitted once the patient is more stable, as long as the results may impact clinical management. (S5-3 - S56)	I	C
Cardiac catheterization should be performed in a tertiary center with sufficient experience in the diagnosis and treatment of children with PH. (S5-3,S5-7–S5-10)	I	C
AVT should be performed in experienced pediatric heart centers able to manage potential complications such as PH crisis, potentially requiring extracorporeal membrane oxygenation (depending on disease severity). (S5-7–S5-9)	I	C
At the day of cardiac catheterization, PAH-targeted pharmacotherapy should be continued (i.e., before and after the procedure). (S5-4–S5-11)	I	C
Cardiac catheterization for the diagnosis of PH should include AVT.(S5-3–S5-5,S5-12,S5-13)	I	C
AVT to assess prognosis and indication for specific PH therapy in children with IPAH/HPAH: the hemodynamic change that defines a positive response to AVT in PH without a cardiovascular shunt is a $\geq$ 20% fall in both mean PAP and PVR/SVR ratio without a decrease in cardiac index*. (S5-5,S5-14)	IIa	C
AVT to assess operability of PAH-CHD (significant shunt) in children: the hemodynamic change that defines a positive response to AVT in PH with significant left-to-right shunt (Qp:Qs > 1.5:1) is a $\geq$ 20% fall in both PVRi and PVR/SVR ratio with final values < 6 WU $\times$ m^2 and < 0.3, respectively. (S5-15–S5-18)	IIa	C
Hemodynamic indicators of PH severity are PVR/SVR ratio and PVRi, rather than percent fall in mPAP during AVT. Moderate and severe PH with high PVR/SVR ratio and high PVRi requires advanced, upfront combination therapy. (S5-1)	I	C
In patients with single ventricle physiology (Fontan, no sub-pulmonary ventricle), a TPG > 6 mm Hg indicates elevated PVR and presence of PVD, and may be considered as indication for vasodilator therapy (S5-19,S5-20)	IIb	C
The patient's level of consciousness during cardiac catheterization should be consistent in subsequent invasive assessments. (S5-4, S5-5)	I	C
Cardiac catheterization in children with suspected or confirmed PH should be performed in spontaneously breathing patients (either awake or moderately sedated) whenever possible. (S5-3,S5-10)	I	C
The effect of supplemental oxygen and hyperoxia on VO_2, dissolved oxygen, and hemodynamic calculations (e.g., Fick equation) must be considered. (S5-21)	I	C
AVT should be performed using iNO; the combination of iNO with oxygen improves pulmonary hemodynamics greater than iNO alone. (S5-22)	I	B
AVT with an initial combination of nitric oxide (20–80 ppm) plus high oxygen (FiO_2 0.8–1.0) is reasonable and shortens the AVT study time. (S5-23)	IIa	C
In children with parenchymal/interstitial lung disease (Group 3 PH), it is reasonable to test several conditions sequentially, including room air, oxygen (FiO_2 1.0), and oxygen (FiO_2 1.0) + iNO (60–80 ppm). (S5-5)	IIa	C
The use of calcium channel blockers, IV epoprostenol, or IV adenosine in AVT is not recommended in children and may be harmful. (S5-24,S5-25)	III harm	C
Inhaled iloprost for AVT in children with PH is a potential alternative if iNO is not available. (S5-26,S5-27)	IIa	C
Repeat cardiac catheterization in children with PH/PAH should be considered in case of clinical deterioration and for assessment of treatment effect, detection of early disease progression, and listing for lung transplantation.	IIa	C
Intervals for repeat catheterizations should be based on clinical judgment but are mainly determined by any clinical worsening, significant change in pharmacotherapy (e.g., drug class), or failure to reach treatment goals.	I	C
It may be reasonable to have a stable patient with PH on PAH-targeted therapy undergo cardiac catheterization every 12–24 months, after a full non-invasive evaluation has been conducted (functional class, 6MWT, echocardiogram, serum NT-proBNP).	IIb	C

6MWT, 6-minute walk test; AVT, acute vasoreactivity testing; COR, class of recommendation; FiO_2, fraction of inspired oxygen; HPAH, heritable pulmonary arterial hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LOE, level of evidence; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension with congenital heart disease; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qp, pulmonary flow; Qs, systemic flow; RHC, right heart catheterization; SVR, systemic vascular resistance; TPG, transpulmonary gradient; VO_2, oxygen consumption; WU, Wood unit.

The above recommendations relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and were based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S5-1 to S5-27) on the above subtopic can be found in the Supplementary Material online. For hemodynamic definitions, invasive measures and their clinical implications, see Supplementary Table S3 online. *It should be noted that the World Symposium on Pulmonary Hypertension 2018 has recommended the use of the Sitbon criteria for a positive AVT in children with IPAH/HPAH, as defined by a decrease in mPAP by at least 10 mm Hg to an mPAP value below 40 mm Hg without a fall in cardiac output.[12] However, most of the European Pediatric Pulmonary Vascular Disease Network's voting group found that there is insufficient evidence for such a recommendation in children and preferred to continue to recommend the modified Barst criteria that define a positive AVT, as outlined in the above table. It should also be noted that there is inaccuracy in the published literature on the cut off values that define the different types of PH (pre-capillary, isolated post-capillary, and combined pre- and post-capillary PH) and mPAP cut off values for AVT, mostly because of inaccurate use of mathematical symbols (> vs. $\geq$ and < vs. $\leq$).

Table 6 Recommendations on the Use of CMR and CT in Children with Suspected or Confirmed PH

Recommendations	COR	LOE
CMR without general anesthesia/deep sedation is recommended in children with suspected PH as part of the diagnostic evaluation and during follow-up to assess changes in ventricular function and chamber dimensions in centers versed and equipped to perform advanced pediatric CMR. (S6-1—S6-4)	I	B
If deep sedation or general anesthesia is required for CMR in a child with PH, the risks and benefits of the diagnostic procedure must be critically reviewed in advance.	I	C
It is recommended that a CMR study of a child with suspected PH should include the following modes of imaging (•): • Cine CMR for the assessment of biventricular mass, volume, and function, using a stack of axial or short axis slices covering the entire heart. (S6-1,S6-2)	I	B
• Phase contrast CMR measurements at the MPA, RPA, LPA, and AAO. (S6-2)	I	B
• Standard 2D flow (phase contrast CMR) measurements at the pulmonary veins may be of benefit in the assessment of pulmonary blood flow. (S6-4)	IIb	C
• LGE can be beneficial for the identification and quantification of myocardial fibrosis. (S6-5)	IIb	C
• Regional RV myocardial function determination might be reasonable by CMR tagging techniques (uncertain yield).	IIb	C
• Simultaneous CMR assessment of biventricular function and ECG may be useful to detect interventricular and LV dyssynchrony that have an impact on cardiac performance. (S6-6, S6-7)	IIb	C
• Non-invasive estimation of RV afterload variables including RVP/PAP/PVR using different proposed CMR techniques may be beneficial when other abnormal anatomical connections are excluded (not well established: interventricular septal position, flow measurements, pulmonary distensibility and elastance, RV-PA coupling). (S6-3)	IIb	C
High resolution chest CT with angiography is recommended in the initial assessment of a child with suspected PH (lung parenchyma/interstitium, MPA/AO ratio, PA pruning, pulmonary veins). (S6-8)	I	C
A CT-measured ratio of the MPA to AAO diameters ≥ 1.3 may be useful to raise the suspicion of PAH in children. (S6-8)—(S6-9)	IIb	C
When the etiology of PH is obvious (e.g., a left-to-right cardiovascular shunt), a chest CT may not be necessary when other abnormal anatomical connections are excluded.	IIb	C
In a PH patient being evaluated for lung transplantation, a high-resolution chest CT is indicated. (S6-10)	I	C

2D, two dimensional; AAO, ascending aorta; AO, aorta; CMR, cardiac magnetic resonance imaging; COR, class of recommendation; CT, computed tomography; ECG, electrocardiography; LGE, late gadolinium enhancement; LOE, level of evidence; LPA, left pulmonary artery; LV, left ventricle; MPA, main pulmonary artery; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RPA, right pulmonary artery; RV, right ventricle; RVP, right ventricular pressure.

The above recommendations relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and were based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S6-1 to S6-10) on the above sub-topic can be found in the Supplementary Material online.

Table 7 Recommendations on the Use of Genetic Testing and Biomarkers in Children with PH

Recommendations	COR	LOE
Genetic counseling is recommended for families with children diagnosed with IPAH or HPAH. (S7-1—S7-5)	I	B
Genetic counseling, if indicated, should be performed by a qualified individual with training in genetics and should precede genetic testing. Information on the disease and possible treatment options, prognosis, and psychosocial issues should be addressed. (S7-6)	I	C
Families of patients with syndromes associated with PAH should be educated on the symptoms of PAH. It is recommended to seek clinical evaluation if the child should develop symptoms of PAH.	I	C
Genetic testing for PAH-associated genes such as *ACVRL1, ABCC8, BMPR2, CAV1, ENG, TBX4, KCNK3,* and *EIF2AK4* can be useful in children with PAH of unknown cause to allow definition of PAH etiology, estimation of prognosis, and identification of family members at risk. (S7-2,S7-5—S7-10)	IIa	B
Genetic testing for the PAH-associated genes *NOTCH3*, *SMAD9*, *GDF2*, *AQP1*, *SMAD8*, *SOX17*, and *ATP13A3* may be useful in children with PAH of unknown cause and identification of family members at risk, although further evidence is needed to confirm pathogenicity of these mutations. (S7-1), (S7-11)	IIb	B
Children who are asymptomatic PAH mutation carriers should be screened with echocardiograms every 1—3 years for the presence of elevated RV pressure, and subsequently undergo additional diagnostic evaluation if clinically indicated.	I	C
Genetic testing of first-degree relatives of an index patient with PAH and a known disease-causing mutation is indicated for risk stratification and rationalizing surveillance.	I	C
Asymptomatic first-degree relatives of patients with HPAH without an identified PAH-associated gene mutation should be screened with serial echocardiograms for the presence of elevated RV pressure, and subsequently undergo additional diagnostic evaluation if clinically indicated.	I	C

(*continued*)

Table 7 (*Continued*)

Recommendations	COR	LOE
Family members of an IPAH/HPAH patient who develop new cardiorespiratory symptoms should be evaluated immediately for PAH.	I	C
Genetic panel testing (NGS) for PAH should be considered to maximize genetic coverage. (S7-2)	IIa	C
Genetic testing for PAH-associated genes may be considered in patients with CHD/cardiovascular shunt and out of proportion PAH (e.g., PAH with small atrial shunt) and should then include *SOX17*. (S7-9)	IIb	C
Genetic testing for PAH-associated genes (including *SOX17*) may be considered in patients with PAH-CHD s/p repair (shunt closure). (S7-10)	IIb	C
Genetic testing for PAH-associated genes may be considered in patients with drug-induced PAH. (S7-12)	IIb	C
Serial measurements of the natriuretic peptides BNP or NT-proBNP are recommended to evaluate disease severity, disease progression, and treatment response in patients with PH. (S7-13—S7-15)	I	B
Measurement of uric acid concentration in blood plasma/serum may be useful to evaluate disease severity. (S7-16)	IIb	C
Analysis of CECs can be useful to stratify operative risk or to evaluate for progression of disease and/or response to therapy in children with PAH. (S7-17, S7-18)	IIa	B
Measurement of circulating endothelin-1 (serum, plasma) is probably not a useful marker of hemodynamics in children with PH. (S7-19, S7-20)	IIb	B
Determination of serum/plasma cardiac troponin (scTnI, hscTNT) might be useful in children with PAH-CHD as a biomarker for PVD severity/RV pressure afterload. (S7-21)	IIa	C
Determination of certain circulating miRNA (plasma, serum) may be useful as indicators of trans-RV and transpulmonary pressure gradients and acute vasoreactivity. (S7-22,S7-23)	IIb	C

BNP, brain natriuretic peptide; CEC, circulating endothelial cell; CHD, congenital heart disease; COR, class of recommendation; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LOE, level of evidence; miRNA, microRNA; NGS, next-generation sequencing; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension with congenital heart disease; PH, pulmonary hypertension; PVD, pulmonary vascular disease; RV, right ventricle; s/p, status post.

The above recommendations relate to the grading system by the European Society of Cardiology and the American Heart Association and are based on pediatric data only (COR, LOE). The complete list of references (S7-1 to S7-23) on the above sub-topic can be found in the Supplementary Material online. A general diagnostic algorithm is provided in Figure 1.

Table 8 Recommendations on the Evaluation and Management of PH in Children and Young Adults with CHD (PAH-CHD, PHVD-CHD)

Recommendations	COR	LOE
All patients with relevant PAH-CHD should receive and benefit from tertiary care. (S8-1, S8-2)	I	C
Children/young adults with clinically suspected CHD should undergo specific TTE screening for PAH and/or ventricular dysfunction. TTE cannot consistently distinguish between PH with increased PVR and PH without elevated PVR. (S8-1—S8-11)	I	C
In children and adolescents with PAH-CHD/PHVD-CHD, a complete diagnostic work-up needs to be performed to determine whether PAH is associated with or causally related to concomitant CHD. (S8-1—S8-3) For indications of cardiac catheterization in children/young adults with CHD and cardiovascular shunt, see Table 5 and Figure 3.	I	C
Defect closure in the presence of PAH-CHD and left-to-right shunting should be based on short- and long-term benefits and not on feasibility of closure.	I	C
Operability/Catheter Intervention (Figure 3): Surgery or interventional closure for CHD with simple post-tricuspid shunts (VSD, PDA) and significant left-to-right shunting should ideally be performed within the first 6 months of life. (S8-12, S8-13)	I	C
Operability/Catheter Intervention (Figure 3): Interventional or surgical closure of simple pre-tricuspid shunts (ASD, sinus venosus defect) and significant left-to-right shunting (Qp:Qs > 1.5) is semi-elective, requires individual decision-making, and is usually pursued at pre-school or school age (5 years and older). (S8-12, S8-13)	IIa	C
Operability/Catheter Intervention (Figure 3): Patients with moderate to large pre- or post-tricuspid shunt lesions and evidence of low-volume left-to-right shunting (i.e., PH out of proportion to the magnitude of cardiovascular shunting), must be considered to have PVD (elevated PVR), and thus should undergo right and left heart catheterization before any intervention/surgery. (S8-3, S8-12, S8-13)	I	C
Operability (Figure 3): Children with PAH-CHD and significant left-to-right shunting, congestive heart failure (pulmonary congestion), failure to thrive, and $SpO_2 > 95\%$ (lower extremities) can be considered operable for shunt closure in infancy; however, peri-operative PH crisis may occur. (S8-13)	IIa	C
Operability/Catheter Intervention (Figure 3): Children with CHD and simple shunt defects (VSD, PDA) beyond the typical timing of surgery (>6 months old), or those not fulfilling the above criteria (heart failure/pulmonary congestion, failure to thrive, and SpO2 > 95% at lower extremities), that is, particularly those with shunt(s) and cyanosis, should undergo comprehensive right and left heart catheterization before any intervention/surgery. (S8-13, S8-15, S8-16)	I	C

(*continued*)

Table 8 (*Continued*)

Recommendations	COR	LOE
Operability/Catheter Intervention: Children with PAH-CHD, with or without significant left-to-right shunting and uncertainties regarding abnormalities in PVR and/or ventricular compliance, are recommended to undergo comprehensive right and left heart catheterization regardless of the patient's age. Indications for cardiac catheterization may be modified in middle- to low-income regions (Table 12). Comorbidities with increased risk for PH with increased PVR (PHVD, PAH with PVD) include genetic syndromes such as trisomy 21. (S8-1, S8-13—S8-16)	I	C
Children with PVRi < 6 WU × m^2 and a PVR/SVR ratio < 0.3, in the absence of additional risk factors, are eligible for standard management/surgical shunt closure/percutaneous interventional device closure (Figure 3 and Table 5). (S8-13)	I	C
Children with PVRi ≥ 6 WU × m^2 and a PVR/SVR ratio ≥ 0.3 should be evaluated by AVT (Figure 3 and Table 5). (S8-13, S8-17).	I	C
Individual patient assessment in tertiary pediatric PH centers is particularly needed when PVRi is between 6 and 8 WU × m^2 (gray zone) (Figure 3 and Table 5). (S8-13)	I	C
A treat-to-close (treat-and-repair) approach (defined as PAH-targeted pharmacotherapy with 1—2 medications followed by partial or complete defect closure) might be considered in highly selected patients with pre- or post-tricuspid shunt (ASD, VSD, PDA) from the gray zone (PVRi 6—8 WU × m^2), and potentially even in children with PAH with PVRi > 8 WU x m^2, with the goal to decrease PVRi << 8 WU x m^2. After (complete or partial) closure, such patients must stay under long-term tertiary follow-up and be reassessed by cardiac catheterization, in addition to non-invasive measures, to assess for PVR after shunt closure. (S8-13, S8-18)	IIb	C
A partial defect closure (fenestrated patch or device) may be considered in selected patients with PAH-CHD from the gray zone (PVRi 6—8 WU × m^2), with or without preceding treat-to-close (treat-and-repair) approach. The impact of PVR numbers alone for clinical decision making differs between patients at different ages (e.g., infants with VSD vs young adults with ASD). (S8-18—S8-20)	IIb	C
Alternatively, PA banding may be considered in selected patients with PAH-CHD with a large post-tricuspid shunt (VSD, complete AVSD = complete AVC) as an alternative to partial defect closure, especially when there is complex cardiac anatomy (e.g., straddling AV-valve) in infancy or significant comorbidity (e.g., genetic syndrome).	IIb	C
When a high-risk patient from the gray zone (PVRi 6—8 WU × m^2) with an intracardiac shunt (AVSD), and additional small PDA undergoes complete closure of the intracardiac defect, it may be considered to leave the PDA open for optional future RV-decompressing interventions (PDA balloon dilation/stenting). (S8-18)	IIb	C
A cardiovascular shunt defect (ASD, VSD, PDA) generally must not be closed when PVRi > 8 WU × m^2 in children (PVR >4.6 WU in adults). (S8-13, S8-21, S8-22)	III harm	C
Patients with Eisenmenger syndrome (Box 1) are usually inoperable irrespective of age with the exception of transplantation. Targeted PAH pharmacotherapy as single drug (ERA or PDE-5i) or combination therapy (sequential or upfront) is safe and can be offered to all patients with established Eisenmenger syndrome, aiming for best possible functional class. If monotherapy is chosen, the currently available data suggests the use of bosentan (ERA) as first-line therapy (COR B for adolescents and young adults). (S8-21—S8-23, S8-27—S8-31).	IIa	B
Patients with Eisenmenger syndrome should be routinely screened for iron deficiency and be given supplementary iron (per os, IV) if needed. (S8-23—S8-34)	I	C
In patients with Eisenmenger syndrome, supplemental oxygen may be considered to reduce symptoms, after careful examination (when PaO_2 < 60 mm Hg). (S8-18, S8-35, S8-36)	IIb	C
In patients with Eisenmenger syndrome and neurological symptoms (minor stroke, stroke), phlebotomy may be considered in severe hyperviscosity syndrome (hematocrit ≥ 70%). (S8-18, S8-24, S8-25) However, iron deficiency from frequent phlebotomies must be avoided. (S8-24)	IIa	C
Phlebotomy should be limited to relieving hyperviscosity symptoms in patients with compensated erythrocytosis. Phlebotomy should not be used to maintain the hematocrit at an arbitrary threshold.	III harm	C
In patients with Eisenmenger syndrome, anti-coagulation may be considered on an individual basis, balancing the risks of thrombosis vs bleeding. Usually only in cases of documented thrombosis, embolism, or atrial fibrillation/atrial flutter is oral anti-coagulation initiated in this age group. (S8-18, S8-29, S8-30, S8-37, S8-38)	IIb	C
In children/young adults with both PAH-CHD/PHVD-CHD and pulmonary congestion, either because of left heart obstruction (mitral stenosis, LVOTO, or CoA) or secondary because of myocardial (LV diastolic) dysfunction, it is recommended to perform a full hemodynamic evaluation by comprehensive right and left heart catheterization. (S8-1, S8-2, S8-39, S8-40)	I	C
In children/young adults with single ventricle physiology, the hemodynamic threshold for operability pre-Fontan surgery is probably a mean TPG ≤ 6 mm Hg (with reasonably low/acceptable end-diastolic pressure of the systemic ventricle). (S8-1, S8-2).	IIa	C

(*continued*)

Table 8 (*Continued*)

Recommendations	COR	LOE
In clinically asymptomatic children/young adults with single ventricle physiology and total cavopulmonary connection (Fontan circulation, no sub-pulmonary ventricle), a PVRi < 3 WU × m^2 and mean TPG < 6 mm Hg is consistent with acceptable hemodynamics. (S8-1)	IIa	C
Children/young adults with total cavopulmonary connection (Fontan circulation) and signs of PHVD (surrogate: mean TPG > 6 mm Hg), low Qp, and/or hepatic congestion should undergo complete diagnostic work up, including comprehensive cardiac catheterization. (S8-1, S8-2, S8-41—S8-43)	I	C
In children/young adults with total cavopulmonary connection (Fontan) and PHVD (TPG is > 6 mm Hg), targeted PH therapies (ERA, PDE-5i, inhaled iloprost) should be considered to improve exercise capacity. (S8-1, S8-44—S8-47)	IIa	C
In children/young adults with total cavopulmonary connection (Fontan) and symptoms—irrespective of hemodynamics (mTPG)—targeted PH therapies (ERA, PDE-5i, inhaled iloprost) may be considered to improve exercise capacity. (S8-1, S8-44—S8-47)	IIb	C

ASD, atrial septal defect, AV, atrioventricular; AVC, atrioventricular canal; AVSD, atrioventricular septal defect; AVT, acute vasoreactivity testing; CoA, coarctation of the aorta; CHD, congenital heart disease; ERA, endothelin receptor antagonist; LV, left ventricle; LVOTO left ventricular outflow tract obstruction; mTPG, mean transpulmonary gradient; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension with congenital heart disease; PaO_2, partial pressure of oxygen; PDE-5i, phosphodiesterase-5 inhibitor; PDA, persistent ductus arteriosus; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PHVD-CHD, pulmonary hypertensive vascular disease with congenital heart disease; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qp, pulmonary flow; Qs, systemic flow; RV, right ventricle; SpO_2, peripheral capillary oxygen saturation; SVR, systemic vascular resistance; TPG, transpulmonary gradient; TTE, transthoracic echocardiography; VSD, ventricular septal defect; WU, Wood unit.

The above recommendations relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and were based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S8-1 to S8-47) on the above sub-topic can be found in the Supplementary Material online. An algorithm for the management of PAH-CHD and a tabular list of PAH medications is provided in Figure 3 and Supplementary Table S5 online.

Table 9 Recommendations for Supportive Measures and Pharmacotherapy in PPHN and PH Associated with BPD/Neonatal CLD

Recommendations	COR	LOE
The term or preterm newborn infant should receive oxygen, ventilatory support and/or surfactant if needed to achieve a pre-ductal SpO_2 between 91% and 95% when PH is suspected or established. It is useful to avoid lung hyperinflation and atelectasis, or lung collapse and intermittent desaturations below 85%, or hyperoxia with pre-ductal SpO_2 above 97%. (S9-1)—(S9-3)	I	B
In a newborn infant with acute PPHN in the first hours after birth, a $PaCO_2$ between 45 and 60 mm Hg and a target pH > 7.25 with lactate < 5 mmol/L may be considered as target values. (S9-1—S9-3).	IIb	B
Intratracheal surfactant should be considered for the preterm and term neonate with PPHN and pulmonary diffusion impairment (but without congenital diaphragmatic hernia) to optimize ventilation and oxygenation (e.g., a newborn with meconium aspiration syndrome and PPHN). (S9-4, S9-5)	IIa	B
It is not well established that iNO in preterm infants below 34 weeks of gestation with respiratory failure reduces the incidence of BPD (S9-6).	IIb	C
iNO administration may be considered in preterm infants below 34 weeks of gestation with respiratory failure and confirmed PH. (S9-7)	IIb	C
iNO is indicated for treatment of PPHN in mechanically ventilated term and near-term newborn infants to improve oxygenation and to reduce the need for ECMO (i) if PaO_2 is less than 100 mm Hg (while receiving 100% oxygen) or (ii) if the oxygenation index exceeds 25. (S9-8)	I	A
Milrinone treatment may be considered as an additional therapy or alternative to iNO if systolic ventricular function is compromised in PPHN. (S9-9, S9-10)	IIb	C
Oral sildenafil is reasonable for treatment of PPHN and PH in BPD, especially if iNO is not available. (S9-11)	IIa	B
Intravenous sildenafil may be reasonable for treatment of PH, including PPHN, in critically ill patients, especially in those with an unsatisfactory response to iNO. (S9-12, S9-13)	IIb	B
Intravenous sildenafil is effective for iNO weaning in treatment of PH, including patients with PPHN.	I	C
In the neonate with PPHN or BPD, intravenous prostacyclin or prostanoids, through a dedicated central line, or inhaled iloprost or inhaled epoprostenol, can be beneficial. (S9-14—S9-17)	IIa	B
The preterm and term neonate with severe PH (PPHN) should receive PGE1 or PGE2 to maintain ductal patency in right heart failure, in the absence of a significant post-tricuspid unrestrictive shunt (e.g., large VSD).	I	C
Endothelin receptor antagonists may be effective in treatment of PPHN in term and late preterm infants. (S9-18).	IIb	C
It may be indicated to extend the treatment of severe PPHN to ECMO if other intensive care measures fail. (www.elso.org) (S9-19, S9-20)	IIa	B
ECMO can currently not be recommended for the preterm infant < 34 gestational weeks (0/7 days) and/or < 2000 g body weight with severe PH. (S9-19, S9-20).	III harm	B

(*continued*)

Table 9 (*Continued*)

Recommendations	COR	LOE
In infants with severe BPD with or without PH, judicious fluid management is important, and may include treatment with diuretics (i.e., hydrochlorothiazide and spironolactone), as long as cardiac pre-load is adequate. (S9-21, S9-22)	IIa	B
Preterm infants at risk for BPD and associated PH may be echocardiographically screened for PH as early as day-of-life 7. (S9-23)	IIb	B
At the time of BPD diagnosis, an echocardiogram should be performed.	I	C
Echocardiographic evaluation for PH is indicated in all infants with BPD/supplemental oxygen at a corrected age of 34—36 weeks' gestation and before hospital discharge.	I	C
It should be attempted to rule out pulmonary vein stenosis before any vasodilatory therapy is initiated in newborn infants with PH. (S9-24, S9-25)	IIa	B
All infants with proven or suspected PH should receive close follow-up, including pre- and post-ductal SpO_2 measurements, echocardiography (1 per week initially, then 1—2 per month), and laboratory work-up depending on disease severity including NT-proBNP (troponin optional), guided by clinical improvement or lack thereof. (S9-1, S9-26, S9-27)	I	C
Low-dose sildenafil is reasonable in children with PH associated with BPD (S9-28), although prospective studies in this population are lacking. (S9-29)	IIa	B

BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; COR, class of recommendation; ECMO, extracorporeal membrane oxygenation; LOE, level of evidence; iNO, inhaled nitric oxide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PGE, prostaglandin E; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; SpO_2, peripheral capillary oxygen saturation; VSD, ventricular septal defect.

The above recommendations relate to the grading system by the European Society of Cardiology and the American Heart Association and are based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S9-1 to S9-29) on the sub-topic above can be found in the Supplementary Material online.

Table 10 Recommendations on the Therapy of Acute PH in the Pediatric ICU—Pharmacotherapy and Mechanical Circulatory Support

Recommendations	COR	LOE
Oxygen should be given when the transcutaneous oxygen saturation is < 95% in children with PH and normal cardiac anatomy.	I	C
Intravenous prostanoids should be considered to treat children with severe PH. (S10-1, S10-2)	IIa	B
iNO may be considered for treatment of post-operative PH in mechanically ventilated patients to improve oxygen-ation and reduce the risk of pulmonary hypertensive crisis. (S10-3, S10-4)	IIb	B
Concomitant sildenafil should be administered to prevent rebound PH in patients who have signs of increased PAP on withdrawal of iNO and require restart of iNO despite preceding gradual weaning of iNO. (S10-5—S10-8)	I	B
Oral tadalafil can be considered as a therapeutic alternative to oral sildenafil in infants and children with signs of increased PAP (see recommendation above). (S10-9)	IIb	B
Intravenous sildenafil may be considered for treatment of PH in critically ill patients, especially in those with an unsatisfactory response to iNO. (S10-8) Intravenous sildenafil reduced PAP and shortened time to extubation and ICU stay in children with post-operative PH. (S10-8)	IIb	C
Inhaled iloprost may be as effective as iNO in children with post-operative PH. (S10-10—S10-12)	IIb	B
In children who develop signs of low cardiac output or profound pulmonary failure despite optimal medical therapy, extracorporeal life support may be considered as bridge to transplantation or recovery. (S10-13)	IIb	C

COR, class of recommendation; ICU intensive care unit; iNO, inhaled nitric oxide; LOE, level of evidence; PAP, pulmonary artery pressure; PH, pulmonary hypertension.

This table summarizes the actual treatment recommendations of acute PH in the pediatric ICU. The above recommendations of the European Pediatric Pulmonary Vascular Disease Network relate to the grading system by the European Society of Cardiology and the American Heart Association and are based on pediatric data only (COR, LOE). The complete list of references (S10-1 to S10-13) on the above sub-topic can be found in the Supplementary Material online.

Table 11 Treatment of Pediatric PH

Recommendations	COR	LOE
Oxygen therapy is reasonable in hypoxemic PH patients who consistently have oxygen saturations < 92% or PaO_2 < 60 mm Hg (S11-1)	IIa	C
Oxygen can be particularly useful for children with PH and an element of parenchymal/interstitial lung disease (e.g., bronchopulmonary dysplasia/neonatal CLD). (S11-2)	IIa	B
Oxygen may be useful for patients with an intrapulmonary shunt and important for PH patients while at altitude or during air travel.	IIb	C
Based on PAH and heart failure studies in adults, mineralcorticoid receptor blockade with spironolactone or eplerenone may be beneficial in PAH patients by improving RV and LV diastolic function. No data or significant experience on eplenerone in children with PAH are available. (S11-3—S11-5)	IIb	C
Diuretic therapy may be considered for selected pediatric patients with PH, that is, those with confirmed fluid overload and/or significant left-to-right shunt.	IIb	C
Diuretic therapy should be initiated cautiously because patients with PH and high PVR often are pre-load dependent to maintain an optimal cardiac output. (S11-4)	I	C
The benefit of **chronic anticoagulation** (warfarin, phenprocoumon) in children with PAH is unclear (so far not studied in children).	IIb	C
Chronic anti-coagulation can be useful in patients with progressive IPAH/HPAH (empirical goal Rs 2.0-INR2.5), patients with CTEPH, patients in low cardiac output, and those with hypercoagulable states.	IIa	C
Indication for **anti-coagulation** should be critically reviewed, especially in small children prone to hemorrhagic complications. In these cases, anti-platelet therapy (e.g., ASA) may be an alternative.	IIb	C
Anti-coagulation, but also anti-platelet therapy (e.g., ASA), should be very critically reviewed in those children prone to hemorrhagic complications because of platelet dysfunction, such as congenital or acquired von Willebrand syndrome (flow/shear stressed induced hemostatic defects), or concomitant PCA therapy (IV/SC treprostinil or IV epoprostenol), as anti-coagulation or anti-platelet therapy may cause harm in these settings. (S11-6)	III harm	C
Accordingly, **anti-coagulation** is potentially harmful in children with HHT or portopulmonary hypertension.	III harm	C
Before starting PAH-targeted therapy for chronic PH, **vasodilator responsiveness** should be determined by **cardiac catheterization**; particularly, anatomical obstruction from pulmonary venous disease or from left-sided heart disease should be excluded in this setting. (S11-4, S11-7)	I	C
CCB: Treatment with CCB (either as monotherapy or in combination with other PAH drugs) should be considered in those patients who have previously been shown to be acutely reactive to iNO ± oxygen during AVT (AVT responders). (S11-7)	IIa	C
For children with a **negative acute vasoreactivity** response, or in those with a failed or non-sustained response to CCBs, risk stratification should probably determine additional PAH-targeted therapy. (S11-7, S11-8)	IIa	C
CCBs are contraindicated in children who have not undergone AVT, in proven non-responders to acute vasodilator testing, and in those with right heart failure, regardless of AVT response. (S11-7, S11-9—S11-11)	III harm	C
Children with PAH and a significant intracardiac left-to-right shunt, and those with Eisenmenger syndrome (i.e., suprasystemic PVR and right-to-left shunt), most likely do not benefit from CCB therapy, regardless of acute vasodilatory response or severity of PHVD, and thus, **CCBs** are not useful in this setting. (S11-7, S11-9, S11-10)	III no benefit	C
Most children with severe PAH are **non-responsive to AVT** (iNO ± oxygen) and should receive targeted therapy other than CCBs. (S11-8, S11-9)	I	C
In the child with mild to moderate chronic PH and lower risk (Figure 2), **initiation of oral goal-targeted therapy** is recommended (Figure 4), regardless of a negative acute vasoreactivity response, and should begin with either a PDE-5i or an ERA, or a combination of PDE-5i and ERA (Supplementary Table S5). (S11-9, S11-12)	I	C
Oral sildenafil can be useful in the setting of iNO weaning in post-operative PH, or in the presence of PH related to parenchymal/interstitial lung disease. (S11-13, S11-14)	IIa	B
High dose **oral sildenafil** treatment (defined in the STARTS-1/-2 trials), either as monotherapy or add-on drug, was associated with a higher mortality rate in children (>8 kg, >1 year old) with PAH/PHVD, including potentially increased mortality. (S11-9, S11-14, S11-15)	III harm	B
IV sildenafil may be considered in neonates with PPHN treated with or without iNO. (S11-16, S11-17)	IIb	C
IV sildenafil may be considered in children with CHD and post-operative PAH/intermittent pulmonary hypertensive crisis, on or off iNO. (S11-9, S11-18)	IIa	B
Early **combination therapy** with two oral PAH-targeted drugs in newly diagnosed (treatment-naive) children with PAH in WHO functional class II-III is reasonable. (S11-9)	IIa	C
In severe (WHO functional class IV) and/or rapidly progressive PAH (diagnosed by cardiac catheterization and non-invasive imaging), continuous IV PCA therapy (i.e., epoprostenol or treprostinil) should be started without delay (start with prostanoid monotherapy or dual/triple combination therapy including PCAs). (S11-9, S11-19—S11-21)	I	C

(*continued*)

Table 11 (*Continued*)

Recommendations	COR	LOE
Start of PCA therapy with IV treprostinil or IV iloprost instead of epoprostenol can be considered in certain circumstances. (S11-9, S11-22, S11-23)	IIa	C
SC PCA therapy (SC treprostinil) may be beneficial in children with severe PAH. (S11-24)	IIa	B
Combination of IV (e.g., epoprostenol or treprostinil) or SC PCAs (treprostinil) with 1 or 2 oral PAH-targeted drugs (e.g., sildenafil, bosentan) may result in better long-term survival in patients with severe PAH.	IIb	C
iNO is mainly used in the ICU setting and useful in patients with acute pulmonary vascular crisis and/or acute exacerbation of PH in the setting of an underlying parenchymal lung disease and/or PPHN. (S11-9, S11-25—S 11-27)	I	B
During the weaning phase of iNO, PH rebound may occur that can be prevented through concomitant use of **oral or IV sildenafil** administration. (S11-28)	I	B
Atrial septostomy (AS), with or without device implantation, preferably resulting in a restrictive interatrial communication, may be considered in patients in functional class III and IV and recurrent syncope under combined medical therapy and as palliative bridge to transplant, increasing the chance for survival while waiting for a donor organ. (S11-29—S11-32)	IIb	C
Based on the risk factors found in an international (adult) study with high procedure-related mortality, **contraindications for AS** include (1) a mean right atrial pressure of >20 mm Hg, (2) resting arterial oxygen saturation <90%, (3) severe RV failure, and (4) patients with impending death. (S11-33)	III harm	C
Based on a small series of children with end-stage PAH, a surgical or interventional anastomosis between LPA and DAO (**reverse Potts shunt**) may be considered as a valuable alternative (destination therapy), or bridge to **bilateral lung transplantation**, in selected cases. (S11-34—S11-39)	IIb	C

AS, atrial septostomy; ASA, acetylsalicylic acid; AVT, acute vasoreactivity testing; CCB, calcium channel blocker; CHD, congenital heart disease; CLD, chronic lung disease; COR, class of recommendation; CTEPH, chronic thromboembolic pulmonary hypertension; DAO, descending aorta; ERA, endothelin receptor antagonist; HHT, hereditary hemorrhagic telangiectasia; HPAH, heritable pulmonary arterial hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LOE, level of evidence; LPA, left pulmonary artery; LV, left ventricle; MR, mineralocorticoid receptor; PaO_2, partial pressure of oxygen; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PCA, prostacyclin analogue; PDE-5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; PHVD, pulmonary hypertensive vascular disease; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; RV, right ventricle; SC, subcutaneous; WHO, World Health Organization.

This table summarizes the current recommendations for the treatment of pediatric PH. The above recommendations of the European Pediatric Pulmonary Vascular Disease Network relate to the grading system by the European Society of Cardiology and the American Heart Association and are based on pediatric data only (COR, LOE). The grading and voting process within the writing group and the complete list of references (S11-1 to S11-39) on the above sub-topic can be found in the Supplementary Material online. For pharmacotherapy, see also Supplementary Table S5 online. Treatment of (i) PAH-CHD (Table 8, Figure 3), (ii) CLD-PH/BPD-PH (Table 9), and (iii) acute PH in the ICU, including mechanical circulatory support (Table 10, Supplementary Table S4 online), are discussed in separate sections of this consensus statement.

Table 12 Recommendations for Diagnosis and Management of PH in Middle and Low Income Regions (MLIRs)

Recommendations	COR	LOE
Children/young adults with suspected or confirmed PH should be referred to, comprehensively evaluated, and treated in specialized pediatric centers. In MLIRs, such pediatric centers often have limited resources and thus children with PH may be referred to centers caring for adult patients with PH.	I	C
The initial evaluation of a child/young adult with PH should include a comprehensive medical history (specifically to identify causes like SCD, tuberculosis, or operability in shunt lesions) and physical examination (MLIR-specific causes like RHD). (S12-1—S12-3)	I	B
Patients in endemic areas of schistosomiasis who present with symptoms and physical signs of PH should undergo a detailed echocardiogram. Patients from such endemic areas with PH and signs of pre-hepatic portal hypertension may be suspected to have schistosomiasis-related PH. (S12-4, S 12-5)	I	C
Patients with schistosomiasis infection and PH may benefit from PAH-directed therapy (mainly sildenafil). (S12-6)	I	C
Patient with active schistosomiasis need treatment with an anti-helmintic drug, such as praziquantel. (S12-7)	I	C
Patients with RHD and PH documented by echocardiography should undergo treatment as per RHD valve treatment guidelines.	I	C
The need for PAH-targeted medications in patients with RHD should be carefully evaluated and eventually pursued only at centers specialized in PH.	I	C
In regions where HIV is highly prevalent, patients with symptoms or signs of PH should undergo a detailed transthoracic echocardiogram to detect PH. (S12-8)	I	C

(*continued*)

Table 12 (*Continued*)

Recommendations	COR	LOE
Patients with HIV infection and PH documented by echocardiography may benefit from PAH-specific therapy (especially bosentan). The role of HAART on the prevalence and outcome of PH secondary to HIV is still controversial. (S12-8—S12-10)	I	C
Treatment with PAH-specific medication (especially sildenafil) in patients with SCD-related PH is controversial and may lead to increases in SCD-related vaso-occlusive crisis. (S12-11)	III harm	C
Patients living at high altitude with symptoms and signs of PH may undergo a detailed transthoracic echocardiogram to detect PH.	I	C
The initial patient history needs to include all major socioeconomic determinants of compliance (profession, family structure, and proximity to treating center). Such information is critical to determine the compliance to treatment and subsequent follow-ups in PH patients. (S-12-2)	I	C
Patients with high altitude—related PH may benefit from PAH-specific medications. (S12-12)	IIa	B
Children < 2 years of age living in MLIRs with PH and so-called simple shunts (ASD, VSD, or PDA) who have normal saturations, signs of increased pulmonary blood flow, and exclusive left-to-right shunt on echocardiography may undergo shunt closure without invasive hemodynamic evaluation. (S12-13, S12-14)	IIb	C
In children with cardiovascular shunt lesions, non-invasive oxygen saturations and arterial PaO_2 during exercise should be measured. A drop in PaO_2 of > 10 mm Hg or SpO_2 by 19% during exercise may indicate an inoperable shunt because of increased PVR. (S12-13—S12-15)	I	C
A comprehensive echocardiogram at diagnosis is recommended as this is the main (and may be the only) modality of diagnosing PH. Features of operability in shunt lesions should also be assessed using echocardiogram. Serial echocardiograms and ECGs may not be feasible in MLIRs (because of lack of expertise and equipment) or cost effective and may be performed on a case-to-case basis. (S12-2, S12-3, S12-16)	I	B
Further imaging (mainly chest CT) is recommended to exclude underlying parenchymal/interstitial lung disease, in ex-premature infants, and in patients with BPD, Down syndrome, or other well-known risk factors. (S12-1, S12-2, S12-13)	I	B
Cardiac catheterization for diagnosis or routine follow-up needs to be done in PH centers only. Lack of expert centers and standardization of cardiac catheterization in MLIRs may lead to erroneous data, wrong data interpretation, or little management value. In absence of vasoreactivity testing, the value of cardiac catheterization (especially if done for shunt operability) is limited. (S12-2, S12-3, S12-17, S12-18)	IIa	B
If no underlying cause of PH is evident, specific tests for HIV, schistosomiasis, and chronic hepatitis (HBV and HCV) should be performed. An abdominal ultrasound is indicated to rule out liver cirrhosis and/or portal hypertension. (S12-2, S12-3, S12-19)	I	B
Serial 6MWTs should include pulse oximetry and are recommended to assess exercise tolerance and response to therapy, and to estimate prognosis in children with PH capable of performing such studies. 6MWT is an inexpensive, reproducible measure of functional capacity. Equipment and expertise for CPET are rarely available in MLIRs. (S12-20)	I	C
PAH-specific therapy is recommended and can significantly improve quality of life. Safety of intravenous therapy in a low-resource setting is also of concern (higher risk of infection and catheter-based complications). Inhalation therapies are often ineffective because of lack of sufficient patient compliance and/or difficulties with applying the devices at home. (S12-2, S12-3, S12-21)	I	B
For children with PH/PHVD undergoing surgery or other interventions requiring sedation or general anesthesia, consultation with cardiac anesthesia and PH service and appropriate post-procedure monitoring is required. (S12-22, S12-23)	I	C
Atrial septostomy and other surgical measures (e.g., reverse Potts shunt) and interventional procedures (ductal stenting, balloon atrioseptostomy) may be considered in highly selected cases at very few specialized centers. These procedures are risky per se and especially in MLIRs, with inconclusive long-term benefits especially in absence of a lung transplant program. (S12-24, S12-25)	IIb	C
Serial measurements of serum NT-proBNP concentration are indicated as changes in NT-proBNP reflect hemodynamic impairment. Cost-benefit assessment of this test is needed in MLIR health care settings. (S-12-26)	IIb	C

6MWT, 6-minute walk test; ASD, atrial septal defect; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; COR, class of recommendation; CPET cardiopulmonary exercise testing; CT, computed tomography; ECG, electrocardiography; HAART, high activity anti-retroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; LOE, level of evidence; MLIR, middle- and low-income region; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PDA, patent ductus arteriosus; PaO_2, partial pressure of oxygen; PHVD, pediatric pulmonary hypertensive vascular disease; PVRi, pulmonary vascular resistance index; PVD, pulmonary vascular disease; RHD, rheumatic heart disease; RV, right ventricle; SCD, sickle cell disease; SpO_2, peripheral capillary oxygen saturation; VSD, ventricular septal defect.

Recommendations specific to MLIRs are predominantly based on expert opinion because of lack of publications from these regions.

Limitations of the 2019 EPPVDN consensus statement on pediatric PH

We acknowledge that most LOE grades of our recommendations on pediatric PH are LOE B or C. Indeed, very few randomized controlled trials have been conducted so far because of the heterogeneity of what is still considered a rare—but underdiagnosed—heterogenous disease in high-income countries. We did discuss the specific complexity of pediatric PH and PAH-CHD in this guideline document. Challenges and future directions in the field (see Box 3) may differ by institution depending on the environment, particularly the medical and economic resources.

Conclusions

This guideline document provides a specific, comprehensive, practical framework for the best clinical care for children and young adults with PH of different etiologies. Although we obtained an increasing set of pediatric data from patient registries and clinical studies and derived conclusions from adult PAH trials, there are still important gaps of knowledge in the field. Nevertheless, advanced therapies, including combination pharmacotherapy and catheter and surgical interventions, are available to children with progressive/severe PAH. Regional differences in the etiology of PH make this a relatively frequent condition in middle to low income regions in which underdiagnosed congenital or acquired cardiac diseases often lead to Eisenmenger syndrome or post-capillary PH in children and young adults. For this reason, it is of utmost importance to raise awareness of pediatric PH in these parts of the world. The high morbidity and mortality, together with the high prevalence of severe PH in such regions with accelerated population growth, underline not only the health care burden but also the unmet need to improve early diagnosis and proper, goal-directed treatment of PH in the young globally.

Take-home messages

The 2019 updated consensus statement of the EPPVDN makes recommendations on established and newly identified diagnostic and monitoring variables, tools, and procedures in pediatric PH. New predictors of outcome have been defined that characterize a child with PH at higher risk (pediatric determinants of risk). In particular, WHO functional class, N-terminal prohormone of brain natriuretic peptide, and tricuspid annular plane systolic excursion have been identified as surrogate variables for survival and thus can serve as treatment goals. A simplified adult PAH risk score based on the 2015 ESC/ERS guidelines emphasizes particularly the prognostic value of mean right atrial pressure, cardiac index, WHO functional class, and N-terminal prohormone of brain natriuretic peptide. A composite end point that consists of death, lung transplantation, or significant disease progression (defined as unplanned PAH-related hospitalization, initiation of intravenous/subcutaneous prostacyclin analogue therapy, and/or WHO functional class deterioration) is probably a feasible end point for clinical trials in pediatric PH. Children with IPAH or HPAH (no significant CHD-shunt) who are true responders to AVT should be treated with calcium-channel blockers (CCBs) such as amlodipine; it should be noted that in patients with poor cardiac function, CCBs should not be used. Close long-term follow-up is required, and combination therapy may be warranted once CCB monotherapy becomes partly inefficient. The evolving strategy of upfront (or early rapid sequence) combination pharmacotherapy may further

Box 3. Challenges and future directions for clinical research in pediatric PH

1. Identification and validation of easy-to-acquire/easy-to-interpret metrics of clinical severity in pediatric PH (Supplementary Figure S1 online).
2. Identification of valid, easy-to-determine treatment goals in pediatric PH (beyond the conventionally used WHO FC, NT-proBNP, TAPSE, and 6MWD). These could include PROs and longitudinal physical activity assessments, such as accelerometry, using wrist bands or other wearables.
3. More seamlessly integrate regulatory requirements, patient recruitment, and clinical trial end points for pediatric PH trials.
4. Initiation of a prospective multicenter study of upfront combination therapy in moderate to severe pediatric PH (combined dual or triple combination).
5. To better determine when and how to perform catheter-based or surgical interventions (atrioseptostomy, reverse Potts shunt procedure) for advanced PH and to further define contra-indications to these procedures and their place and timing in the treatment algorithms.
6. Initiation of investigator-initiated pilot and/or industry-sponsored Phase 2 or 3 studies on the safety and efficacy of new compounds recently published/approved for adult PAH (macitentan, riociguat, selexipag, and treprostinil).[3,14]
7. Gather sufficient data on the use, safety, efficacy, and adverse effects of new drugs in pediatric PH (e.g., selexipag, riociguat).

6MWD, 6-minute walk distance; FC, functional class; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PRO, patient-reported outcome; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

improve outcome of pediatric PAH. Still, based on adult RCTs and pediatric registry data (TOPP, COMPERA KIDS, PPHNet[26]; NCT02610660; NCT01347216; NCT02249923), a high percentage of children with newly diagnosed, moderate to severe PAH are started on suboptimal (mono) therapy (a therapy can be suboptimal even if it is not mono, such as inadequate dosing, inadequate medication etc).

Disclosure statement

All members of the writing group are required to complete and submit a disclosure questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. Each author filled out and signed a form for disclosure of potential conflicts of interests, provided by the International Committee of Medical Journal Editors. None of the authors was financially reimbursed for her/his contributions to this manuscript. The chair and co-chair of this writing group indicate no significant conflicts of interest related to the content of this article. Comprehensive information on conflicts of interest, relationships with industry, and current grant support of all writing group members can be found in Supplementary Table S11 of this article.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2019.06.022.

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Supplementary Appendix

2019 Updated Consensus Statement on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension. The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

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Content: supplementary text, 11 supplementary tables, 3 supplementary figures, supplementary references

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TABLE OF CONTENTS (Supplementary Appendix)

ABBREVIATIONS and ACRONYMS

AS = atrial septostomy
AHA = American Heart Association
AVT = acute pulmonary vasoreactivity testing
BPD = bronchopulmonary dysplasia
CCB = calcium channel blocker
CHD = congenital heart disease
CI = cardiac index
COR = class of recommendation
cGMP = cyclic guanosine monophosphate
CPET = cardiopulmonary exercise testing
DPD = diastolic pressure difference
EMA = European Medicines Agency
EPPVDN = European Pediatric PVD Network
ES = Eisenmenger syndrome
ERS = European Respiratory Society
ESC = European Society of Cardiology
FDA = US Food and Drug Administration
HIV = human immunodeficiency virus
IPAH/FPAH/HPAH = idiopathic/familial/heritable pulmonary arterial hypertension
LAP = left atrial pressure
LOE = level of evidence
LV = left ventricle
MLIRs = middle- and low-income regions
MR = mineralocorticoid receptor
nCLD = neonatal chronic lung disease
NO = nitric oxide
NT-proBNP = NT-pro B-type natriuretic peptide
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PAWP = pulmonary artery wedge pressure
PDA = persistent ductus arteriosus
PDE5 = phosphodiesterase 5
PH = pulmonary hypertension
PHVD = pulmonary hypertensive vascular disease
PPHN = persistent pulmonary hypertension of the newborn
RAP = right atrial pressure
RCT = randomized controlled trial
RV = right ventricle
TPG = transpulmonary pressure gradient
VO_2 = oxygen consumption
WHO = World Health Organization
WSPH = World Symposium on Pulmonary Hypertension

SUPPLEMENTARY TEXT

The European Pediatric Pulmonary Vascular Disease Network

The European Pediatric PVD Network (EPPVDN) is a registered non-profit organization that is independent of any medical-scientific society and industry. The network strives to define and develop effective, innovative diagnostic methods and treatment options in all forms of pediatric pulmonary hypertensive vascular disease (PHVD), including specific forms such as PAH-congenital heart disease (CHD), pulmonary hypertension (PH) associated with bronchopulmonary dysplasia (BPD), persistent PH of the newborn (PPHN), and related cardiac dysfunction.

Class of Recommendation (COR), Level of Evidence (LOE)

The recommendations in this article relate to the grading system for class of recommendation (COR) and level of evidence (LOE) currently proposed by the European Society of Cardiology (ESC) and the American Heart Association (AHA) **(**COR, **Table 1**; LOE, **Table 2)**, and was based on pediatric data only (pediatric studies, or adult studies enrolling > 10% children). The grading and voting process is described further below. A full list of references can be found in this ONLINE SUPPLEMENT. Importantly, health care providers must adhere to the medication labeling and follow future drug recommendations/warnings potentially published by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) when applying these recommendations into clinical practice.

Voting Process

The executive writing group held 2 face-to-face-meetings, 5 teleconferences and multiple Email roundtables, to discuss the individual topics and conduct the voting on the wording of the recommendations and the grading (COR, LOE) thereof. Ultimately, of the 216 graded recommendations, 99 were class (COR) I, 105 were class II (50 COR IIa, 55 COR IIb), and 12 determined as class III (COR III; n = 2 "no benefit" or n = 10 "harm"). One recommendation was level of evidence (LOE) A, 61 were LOE B, and the majority, i.e. 154, were stratified as LOE C, due to the lack of randomized controlled studies.

Peer Review Process

The manuscript has been peer reviewed by several anonymous external experts according the journal's standardized review process for original articles, including 4 anonymous experts selected by the ISHLT scientific committee, one expert assigned by the AEPC, and 2 experts assigend by the ESPR. The chair of the ISHLT S&G committee and the handling editor assigned by the *Journal of Heart and Lung Transplantation* led the peer review process.

Endorsement Process (AEPC, ESPR, ISHLT)

The Association for European Paediatric and Congenital Cardiology (AEPC), endorsed the manuscript on March 18, 2019. The Society for Pediatric Research (ESPR) endorsed the manuscript on April 24, 2019. The International Society of Heart and Lung Transplantation (ISHLT) was actively involved in the peer review process as outlined above, and endorsed the manuscript on May 20, 2019.

SUPPLEMENTARY "S"-REFERENCES

The supplementary references ("S") below refer to the Tables 3-12 in the main manuscript containing recommendations for the diagnosis and treatment of pediatric PH.

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SUPPLEMENTARY TABLES

Table S1. Classification of Pulmonary Hypertension (6th World Symposium on Pulmonary Hypertension, Nice 2018)

Group 1-5 Pulmonary Hypertension	
1. Pulmonary arterial hypertension (PAH)	
1.1 Idiopathic PAH	
1.2 Heritable PAH	e.g. BMPR2, ACVRL1*, TBX4*, ENG, SOX17, KCNK3 and additional genes. See Table 4. (*enriched in pediatric vs. adult PAH)
1.3 Drug and toxin induced	e.g., amphetamines, methamphetamines, dasatinib, toxic rapseed oil
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 disease (CHD) 1.4.5 Schistosomiasis	CHD: of note, PH associated with complex CHD is classified as group 5.4 (see Table S7), and PH due to obstructive post-capillary lesions is classified as group 2.4 PH (see Table S8). For PH associated with HIV or schistosomiasis, see Table 12.
1.5 PAH long-term responders to calcium channel blockers	See main text for acute vasoreactivity testing (AVT).
1.6 PAH with overt features of venous/capillary (PVOD/PCH) involvement	Pulmonary function tests: Decreased DLCO (frequently <50%) Chest HRCT: e.g. Septal lines; Centrilobular ground-glass opacities/nodules Response to PAH therapy: possible pulmonary edema. PVOD/PCH may be associated with EIF2AK4 mutations.
1.7 Persistent PH of the newborn syndrome	See Table S9.
2. Pulmonary hypertension due to left heart disease	2.1 PH due to heart failure with preserved LVEF 2.2 PH due to heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. Pulmonary hypertension due to lung diseases and/or hypoxia	3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed restrictive/obstructive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders (s. Table S10)
4. PH due to pulmonary artery obstructions	4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear multifactorial mechanisms	5.1 Hematological disorders 5.2 Systemic and metabolic disorders 5.3 Others 5.4 Complex congenital heart disease

Table S1. PVOD, pulmonary veno-occlusive disease, PCH, pulmonary capillary hemangiomatosis

Table S2. Classification of Pediatric Pulmonary Hypertensive Vascular Disease (PPHVD) (PVRI, Panama, 2011): 10 Basic categories of PPHVD

#	Basic PPHVD Category
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

Table S2. Ten Basic categories of Pediatric Pulmonary Hypertensive Vascular Disease (PPHVD); Paediatric Taskforce of the Pulmonary Vascular Research Institute, Panama 2011 From *del Cerro Pulm Circ, 2011(1).*

Table S3. Hemodynamic Definitions, Invasive Measures and Clinical Implications

Table S3a. Hemodynamic Definitions of Pulmonary Hypertension		
Definition [a, b, c, d]	**Invasive measures** [a, b, c]	**PH-group**
Pulmonary hypertension (PH) [a, b]	mPAP > 20 mmHg	1-5
Pre-capillary PH [a, b]	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVRi ≥ 3 WU · m^2	1, 3, 4 and 5
• Isolated post-capillary PH (Ipc-PH, as defined for adults) [a, b]	mPAP > 20 mmHg PAWP > 15 mmHg PVRi < 3 WU · m^2 DPD < 7mmHg (adults) [c]	2 and 5
or		
• Combined post-capillary and pre-capillary PH (Cpc-PH, as defined for adults)	mPAP > 20 mmHg PAWP > 15 mmHg PVRi ≥ 3 WU · m^2 DPD ≥ 7mmHg (adults) [c]	2 and 5

Table S3b Invasive Measures and Clinical Implications		
Measure [a-f]	**Abnormality**	**Clinical implications**
Mean RAP	Mean RAP >15mmHg Mean RAP >20mmHg	"Higher risk", RV failure, higher mortality Contraindication for atrial septostomy
mPAP (mmHg) [a, b, e]	mPAP > 20mmHg	Definition of PH (WSPH, 2018)
mPAP/mSAP	mPAP/mSAP >0.3 mPAP/mSAP >0.75	Adjunct criterion for presence of PH Higher mortality
PAWP (mmHg)	PAWP > 15 mmHg	Criterion for post-capillary component [c]
PVR index (Wood units · m^2) [b, e]	PVR index >3 WU · m^2 PVR index >8 WU · m^2 PVR index >15 WU · m^2	Criterion for pre-capillary component [c] Inoperability in PAH-CHD "Higher risk", higher mortality
Cardiac index (L/min · m^2) by Fick principle or thermodilution	CI < 2.5 L/min · m^2	"Higher risk", low cardiac output, higher mortality
SVO_2, %	SVO_2 < 55%	Low cardiac output, higher mortality
Acute vasoreactivity testing [f]	AVT negative	see Tables 5 and 8; Figures 2, 3 and S1

Table S3. Hemodynamic definitions according to 2015 ESC/ERS guidelines on PH (Galie et al Eur Heart J, 2016)(2), modified according to WSPH 2018 (Simonneau G et al. Eur Resp J, 2018)(3).

[a]The definitions of the PH subtypes in table 3a apply only when cardiac index is either normal or decreased (but not in hyperdynamic states with significantly increased cardiac index, e.g. patients receiving high dose prostacycline analogue infusion or those with sepsis).

[b]Of note: The definition of PH has changed to a lower mPAP cut off value (mPAP > 20mmHg) and now also includes a PVR and PVR index cut off value of 3 WU (adults) and 3 WU · m^2 (children) to distinguish pre-capillary from isolated post-capillary PH (Ipc-PH).

[c] Of note: Diastolic transpulmonary pressure gradient (DPG, syn. dTPG) is an adjunct criterion to determine pre- and postcapillary components in adults with PH. DPD (dTPG) has been a criterion in the 2015 ESC/ERS guidelines but was omitted in the WSPH 2018 consensus documents.
[d] Of note: Previous terms such as “reactive PH” or “out of proportion PH” were removed.
[e] It should also be noted that there is inconsistency in the published literature on the cut off values that define the different types of PH (pre-capillary, isolated postcapillary, combined pre- and post-capillary PH>; mPAP, PAWP, PVR, PVR index) and mPAP cut off values for AVT, mostly due to inaccurate use of mathematical symbols (> vs. ≥ and < vs. ≤, for mPAP and PVR).
[f]It should be noted that the WSPH 2018 has recommended the use of the Sitbon criteria for a positive AVT in children with IPAH/HPAH, as defined by a decrease in mPAP by at least 10 mmHg to a mPAP value below 40 mmHg without a fall in cardiac output (Rosenweig EB et al. Eur Resp J, 2018)(4). However, the majority of the EPPVDN’s voting group found there is insufficient evidence for such a recommendation in children, and prefered to continue to recommend the modified Barst criteria that define a positive AVT, as outlined in the above table.
See also Table 5, Table 8, Figure 2 (determinants of risk), Figure 3. (algorithm on PAH associated with congenital heart disease), and Figure S1 (risk score sheet for a child with PH).
Abbreviations: CI = cardiac index; mPAP = mean pulmonary arterial pressure; dPAP = diastolic pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; DPD = diastolic pressure difference (dPAP-PAWP; synonym: diastolic transpulmonary pressure gradient, dTPG).

Table S4: Pharmacotherapy of Acute Pulmonary Hypertension in the Pediatric Intensive Care Unit

Drug	Dose	Comment
Dobutamine	5 – 20 µg/kg/min i.v.	Increases myocardial oxygen consumption, tachycardia. Probably does not increase PVR
Epinephrine	0.01 – 1 µg/kg/min i.v.	Positive inotropy. Increases myocardial oxygen consumption, tachycardia. Moderate effects on PVR and SVR.
Epoprostenol i.v.	Start with 1-3 ng/kg/min, increase gradually in 1-2ng/kg/min increments every 15-120min, depending on acuity, treatment response and adverse effects. Midterm dose up to 60 ng/kg/min i.v. (and even higher doses)	Caution: systemic arterial hypotension. Often need to pause at 10-20ng/kg/min. b/o adverse effects. Short half-life. May need to change drug vial/delivery system every 12-24h (see Table 11)
Iloprost inhalation	0.25 µg/kg inhal, max. 10 µg; 6-9 inhalations/24 hrs. Continuous inhalation has also been applied.	Caution: Systemic arterial hypotension.
Levosimendan	(0.1 –) 0.2 µg/kg/min i.v. over 24 hours; may repeat infusion every 7-14 days	Lowers PVR. Caution: systemic arterial hypotension. Long half-life.
Milrinone	0.3 – 1.0 µg/kg/min i.v.	Lowers PVR. Caution: systemic arterial hypotension.
NO inhalation	2 - 40 ppm continuous inhalation	Monitor Met-Hemoglobin.
Norepinephrine	0.01 – 1 µg/kg/min i.v.	Increases SVR and PVR.
Sildenafil i.v., p.o.	2 (-4) mg/kg/d i.v. (no bolus) 8 - 20 kg BW: 3 x 10 mg p.o. > 20 kg BW: 3 x 20 mg p.o.	In children weighing less than 8 kg, dosage of 1 mg/kg/dose q 6 hrs. (drug not approved, no RCT data)
Terlipressin i.v.	5 – 10 ng/kg/min i.v.	Probably does not increase PVR (advantage vs. norepinephrine).
Treprostinil i.v.	Start with 1-3 ng/kg/min, increase gradually (see Epoprostenol), effective and midterm dose is 2-3-fold higher for treprostinil than epoprostenol.	Caution: Systemic arterial hypotension. Often need to pause at 10-20ng/kg/min. b/o adverse effects. Longer half-life. Implantable pump available for long-term use.
Vasopressin i.v.	0.0003 – 0.002 IU/kg/min i.v.	Probably does not increase PVR (advantage vs. norepinephrine).

Table S4. Pharmacotherapy of acute pulmonary hypertension (PH) in the pediatric intensive care unit (PICU). Many of the above medications are not FDA- or EMA-approved for the use in children. BW, body weight.

Table S5. Oral and Parenteral Pharmacotherapy for Pediatric Pulmonary Arterial Hypertension

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Calcium Chanel Blockers					
Amlodipine	• Only if reactive to vasodilator testing • Do not use in patients with high right atrial pressure or low cardiac output	• Starting dose: 0.1mg/kg/dose (or 1-5 mg/ adult dose), twice daily PO, uptitrate • Maintenance dose: 2.5-10 mg/dose twice daily PO • Max. adult dose 20 mg/day PO	• Decrease in PVR	• Bradycardia • Decreased cardiac output • Peripheral edema • Rash • Gum hyperplasia • Constipation	**COR IIa** **LOE C** • Duration of benefit may be limited even with initial favorable response • Efficacy in Eisenmenger syndrome is rare
Nifedipine	• Only if reactive to vasodilator testing • Do not use in patients with high right atrial pressure or low cardiac output	• Starting dose 0.2-0.3mg/kg/dose three times daily PO, uptitrate • Maintenance dose: 1-2.5 mg/kg/dose twice daily PO • Max. adult dose 120-240mg/day PO in 3 divided doses • May use extended release preparations (max. 180 mg/day PO)	• Decrease in PVR	• Bradycardia • Decreased cardiac output • Peripheral edema • Rash • Gum hyperplasia • Constipation	**COR IIa** **LOE C** • Duration of benefit may be limited even with initial favorable response • Efficacy in Eisenmenger syndrome is rare

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Phosphodiesterase type 5 Inhibitors					
Sildenafil	• Approved for adult PH Group 1 • EMA approved for pediatric PH Group 1 (age>1 year) • FDA warning (2012) and subsequent clarification (2014)	*Oral:* • Starting dose: 0.3-0.5 mg/kg/dose three (e.g., > 1 year old) or four times (e.g., < 1 year old) daily PO • Maintenance dose: 0.5-1 mg/kg/dose three (> 1 year old) or four times (< 1 year old) daily PO • *<8 kg (no RCT data)* Starting dose 0.3-0.5 mg/kg/dose four times daily PO Maintenance dose: 1mg/kg/dose four times daily PO. Maximum dose (controversial): 10mg/dose PO three to four times daily (children) • *European dosing (EMA approved):* 8-20kg: 10mg/dose three times daily PO (less in neonates / infants < 10kg) ≥ 20kg: 20mg/dose three times daily PO *Intravenous:* 2 (-4) mg/kg/day continuous IV infusion; usually no bolus	• Increase in CI • Decrease in PVR • May improve diastolic ventricular function in single and biventricular circulations based on preclinical studies	•. Flushing •. Agitation • Hypotension • Vision and hearing loss are concerning findings in premature infants • Priapism	**COR IIa** **LOE B** **(COR III, LOE B for high dose)** • One pediatric RCT (STARTS-1/-2) • A greater mortality was noted in the STARTS-2 extension study in treatment naïve children treated with high dose sildenafil monotherapy • *STARTS-1/-2 medium dosing regimen with best effect on VO2max was:* 8-20 kg, > 1 year old: 10mg/dose three times daily PO 20.1-45 kg: 20mg/dose three times daily PO > 45 kg: 40mg/dose PO three times daily • FDA warning (2012) and subsequent clarification (2014) of chronic use in children aged 1–17 years • Concomitant use of CYP3A4 inhibitors decreases clearance of sildenafil • Co-administration of bosentan leads to decreased sildenafil concentrations and increased bosentan concentrations (clinical relevance is unclear though) • Use in premature neonates not well studied

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Tadalafil	• Approved for adult PH Group 1 by EMA and FDA in 2009.	• Starting adult dose: 20mg/dose once daily PO • Consider uptitration from 20 to 40 mg/dose once daily PO • Max. adult dose: 40 mg/dose once a day PO • Pediatric maintenance dose probably 1mg/kg/day PO	• Increase in CI • Decrease in PVR	• Side effects similar to sildenafil. • Probably no significant effect on vision	**COR IIa** **LOE B** • Once a day dosing. • Safety and efficacy data in children are limited.
Guanylate Cyclase (GC) Stimulators					
Riociguat	• Approved by EMA and FDA for adult PH Group 1 in 2014: (IPAH/HPAH only) and Group 4 PH (CTEPH) for monotherapy or combination therapy with ERA	• Starting adult dose 1mg three times daily PO, uptitration required • Maintenance adult dose 1-2.5mg (dose three times daily PO • Maximum adult dose 2.5mg/dose three times daily • Limited pediatric data.	• Increase in CI • Decrease in PVR	• Systemic arterial hypotension • Headache, dizziness, dyspepsia • Not to use together with PDE5-inhibitors (sildenafil, tadalafil)	**COR IIb** **LOE C** • Safety and efficacy data in children not available in 2018. • COR I, LOE A for adult PH group 1 and 4

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Endothelin receptor antagonists (ERA)					
Bosentan (dual ET_A and ET_B receptor antagonist)	• Approved by EMA and FDA for adult PH Group 1 • Approved by FDA and EMA for use in children > 1 years old • For patients > 12 years old, a benefit also shown for FC II.	• Starting dose: 0.3-1 mg/kg/dose twice daily, uptitration • <10 kg: max. 2 mg/kg/dose twice daily PO • 10–20 kg: max. 2mg/kg/dose twice daily PO (32 mg tablets) • 20–40 kg: 62.5 mg/dose twice daily PO • > 40 kg: 125 mg/dose twice daily PO	• Increase in CI • Decrease in PVR	• Abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, edema, nasal congestion, anemia. • Not recommended in patients with moderate or severe hepatic impairment • Monthly LFTs required • Incidence of AST/ALT elevation is less in children (3.5%) compared with adults • Teratogenicity and male infertility are risks	**COR IIa** **LOE C** **Eisenmenger:** **COR IIa** **LOE B** • Data have been published on efficacy in Eisenmenger PH. • Caution in concomitant use of CYP3A4 inducers and inhibitors
Macitentan (dual ET1A and ET1B receptor antagonist)	• Approved by EMA and FDA for adult PH Group 1 (IPAH/HPAH only)	• Starting dose (adults): 5 – 10 mg once daily PO • Maintenance adult dose 10mg once daily PO • No published data on pediatric dosing in 2018. • Limited pediatric data.	• Increase in CI • Decrease in PVR	• Class specific side effects are similar to bosentan. • Headache, nasopharyngitis, anemia. • Not recommended in patients with moderate or severe hepatic impairment • Dependent edema may limit usefulness • Teratogenicity and male infertility are risks (decreases in sperm count have been observed)	COR IIb LOE C • RCTs in adults (Pulido et al. SERAPHIN NEJM 2013)(5) • Safety and efficacy data in children not available in 2018. • Caution in concomitant use of CYP3A4 inducers and inhibitors

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Ambrisentan (selective $ET1_A$ receptor antagonist)	• Approved for adult PH Group 1 by FDA and EMA • Use in pediatrics has not been extensively evaluated. • In children >12 years old with intolerance to bosentan, there may be benefit.	• Adult dosing starts with 5 mg daily up to 10 mg daily.	• Increase in CI • Decrease in PVR	• Class specific side effects are similar to bosentan. • Incidence of serum aminotransferase elevation is low • May decrease effectiveness of birth control • Dependent edema may limit usefulness • Teratogenicity and male infertility are risks • No drug–drug interactions between ambrisentan and sildenafil or tadalafil observed	**COR IIa** **LOE C** • Safety and efficacy data in children are limited. • Caution in concomitant use of CYP3A4 inducers and inhibitors

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Prostacyclin Analogues (Prostanoids)					
Epoprostenol	• Approved by EMA and FDA for adult PH Group 1	• Intravenous infusion • Starting dose: 1-2 ng/kg/min IV without a known maximum. • Maintenance dose: 10 – 20 – 50 - 100 ng/kg/min IV • In pediatric patients a stable dose is usually between 50 and 80 ng/kg/min IV at 1 year after start of treatment. • Doses > 150 ng/kg/min IV have been used • Dose increases are required • High output failure at high doses can occur.	• Increase in CI • Decrease in PVR • Increased survival	• Flushing, jaw, foot and bone pain, headaches, nausea and diarrhea • Systemic hypotension is possible • The half-life is short (2–5 min) so PH crises occur rapidly if the infusion is stopped • Ice pack cooling and remixing every 24 h needed for epoprostenol GM • epoprostenol AM does not need ice packs but cassettes need to be changed every 7 days at the latest. • Central line complications (infection, occlusion, extravasation) occur.	**COR I** **LOE B LOE C** • Standard therapy for severe PH (WHC FC class IV) • A "temperature stable" formulation is now available. Epoprostenol sodium with arginine-mannitol excipients (epoprostenol AM; Veletri [Actelion Pharmaceuticals Ltd]) and epoprostenol sodium with glycine-mannitol excipients (epoprostenol GM; Flolan [GlaxoSmithKline]) are intravenous treatments for pulmonary arterial hypertension (PAH). Epoprostenol AM contains different inactive excipients, resulting in greater stability at room temperature compared with epoprostenol GM.
Treprostinil	• Approved by EMA and FDA for adult PH Group 1	*Intravenous or subcutaneous infusion* • Starting dose 1- 2 ng/kg/min without a known maximum. • In pediatric patients a stable dose is usually met between 50 and 80 ng/kg/min IV/SC at 1 year. • Tolerance occurs and dose increases are required initially	• Increase in CI • Decrease in PVR • Improved or unchanged 1-year functional class • Less severe side effects than epoprostenol.	• Flushing, jaw, foot and bone pain, headaches, nausea and diarrhea are common side effects that reoccur after each dose increase. • The frequency and severity of side effects are less than with epoprostenol. • Elimination half-life is 4.5 h with distribution half-life of 40 minutes • The drug is stable at room temperature so it does not require cooling	*For IV / SC* **COR IIa, LOE C (IV),** **COR IIb, LOE B (SC)** • Safety and efficacy data in children are limited. *For intermittent inhalation:* **COR IIb** **LOE C** • The nebulizer requires patient activation and controlled inhalation limited by age and development.

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
		Inhalation (nebulizer, inhaler) • 1–9 patient activated breaths every 6 hours.		• Central line complications (infection, occlusion, extravasation) can occur. • Subcutaneously implanted pumps connected to a central intravenous catheter are available for long-term i.v. use • Subcutaneous injection site pain and possible infection limits this route • Inhaled drug can worsen reactive airway symptoms.	
Iloprost	• Approved for adult PH Group 1	*Intravenous infusion* • Pediatric dosing has not been determined • Intravenous infusion • Starting dose: 1 ng/kg/min IV, uptitrate • Maintenance dose 5-10ng/kg/min IV as tolerated. A maximum i.v. dose has not been described.	• Improved CI • Improved PVR	• Intravenous infusion (rarely used): similar to epoprostenol and trepostinil	*Intravenous infusion* **COR IIb** **LOE C** • In pediatrics, the dosing frequency is not established.
		Inhalation (nebulizer, inhaler) • Nebulizer for children (< ca. 5 years) and small inhaling devices for older children. • Pediatric dosing has not been determined but 6–9 inhalations per day are required, each lasting 8–15 min. • Start with 2.5 mcg/dose (1.25mcg in small children) and uptrate to 5mcg/dose as tolerated • Dose range: Ampules deliver 2.5-5 mcg to the mouth piece		• For inhalation: jaw pain, wheezing; especially at the initiation of therapy • A new chip for the adaptive aerosol delivery (AAD) systems allows now to reduce the duration of inhalations from 10-15 down to 4-5 minutes.	*For intermittent inhalation* **COR IIa** **LOE C** • In pediatrics, the dosing frequency and lack of compliance may limit its use. • Many experts recommend q3h inhalations during the day time for better compliance that can be recorded and monitored with a chip within the inhaler.

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Selexipag (oral use)	• Prostacyclin IP receptor agonist. Pending approval for adult PH group 1 (PAH). Limited pediatric data.	• Adult dosing: Starting dose: 200 mcg PO twice daily. Dosing increase in 200mcg twice daily steps. Max. dose 1.6 mg twice daily PO • No published data on pediatric dosing in 2018. • Limited pediatric data.	• Reduction of morbidity/mortality event. • Improved CI • Improved PVR	• To be determined (RCT and post marketing surveillance pending)	**COR IIb** **LOE C** GRIPHON trial (1,156 PAH patients): Significant risk reduction of morbidity/mortality events.
Mineralcorticoid receptor (MR) antagonists					
Spironolactone	• Improves hepatic congestion and edema. • Inhibits mineralcorticoid receptors and may improve RV and LV diastolic dysfunction	• Loop diuretics, thiazides, and spironolactone are all dosed by weight and not different than for other forms of heart failure.	• Decreased signs of right heart failure	• Hyperkalemia	**COR IIb** **LOE C** • Better outcome of adult PAH patients in post hoc analysis with add-on spironolactone to ambrisentan (ARIES-1/-2) • Better outcome in adult patients with LV diastolic dysfunction/HFpEF. A similar benefit was noted for the oral MR antagonist eplerenone in HFpEF. • see: MR antagonist Epleneron.
Diuretics					
Furosemide (loop diuretic)	• May improve hepatic congestion and edema.	• Loop diuretics, thiazides, and spironolactone are all dosed by weight and not different than for other forms of heart failure.	• Decreased signs of right heart failure • may be overused in PAH	• Caution: moderate to excessive diuresis can reduce the preload of the failing RV, and worsen clinical status	**COR IIb** **LOE C**
Hydrochlorothiazide (thiazide)	• Improves hepatic congestion and edema.	• Loop diuretics, thiazides, and spironolactone are all dosed by weight and not different than for other forms of heart failure.	• Decreased signs of right heart failure	• Care is needed, as over diuresis can reduce the preload of the failing RV.	**COR IIb** **LOE C**

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Inhalative therapies other than prostanoids					
Oxygen	• Helpful for cyanotic patients with an element of CLD or intrapulmonary shunt	• 1–2 L/min by nasal prongs	• Improved sense of well-being	• Too high a flow rate can dry the nares and cause epistaxis or rhinitis.	**COR I COR IIa** **LOE C** • Oxygen is not usually prescribed for children with PH unless day time saturations are low (<92%) • Polysomnography helpful in delineating need for O_2 therapy at night • Oxygen with exertion for patients with clinically significant desaturation with exertion
Nitric Oxide (continuous inhalation)	• PPHN • Acute exacerbation of PAH, including PH crisis • Acute PH in respiratory distress syndrome?	• 0-5 ppm • 20 ppm	• Selective fall in PVR	• Methemoglobin and NO2 at higher doses • Rebound PH on weaning off iNO (risk can be reduced by concomitant use of sildenafil)	**COR I** **LOE B** • Not approved by EMA or FDA for post-operative CHD

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Anticoagulative and Antiplatelet Agents					
Warfarin (Coumadin®), Phenprocoumon (Marcumar®, Falithrom®) (Vitamin K antagonists)	• No definitive studies in children • Oral anticoagulation in patients with a history of thrombosis, hypercoagulation, central lines • Some PH centers use coumadin or warfarin in pediatric IPAH or HPAH	• Individual dosing depends on agent used, co-medication, patient history • Goal INRs in the range of (1.5-) 2.0-2.5 are usually chosen for this indication. • Higher INR may be needed for history of thrombosis or hypercoagulability	• Prevention thrombosis and thromboembolic events	• The risk of anticoagulation in pediatrics must be balanced with the hypothetical benefits. • Teratogenic effects.	**COR IIb** **LOE C** **COR III (harm)** in children prone to hemorrhagic complications. • Use of Coumadin, in children prior to walking well and in children may add risk.
Acetylsalicylic acid (ASA; Aspirin)	Alternative to oral anticoagulation (warfarin, Coumadin) in pediatric IPAH/HPAH, especially in small/active children	• Maintenance dose 2-4mg/kg/dose once daily PO; max. 100mg/dose • Adult dose: 100mg/dose once daily PO	• Inhibition of platelet aggregation, thrombosis, and thromboembolic events	• Usual risks for ASA: bleeding, Reye syndrome, asthma • Combination with clopidogrel or Vitamin K antagonist carries moderate to high bleeding risk	**COR IIb,** **LOE C** **COR III (harm)** in children prone to hemorrhagic complications.
Contraceptives	• Pregnancy in women with moderate to severe PH bares a high risk of maternal and fetal death. • Endothelin receptor antagonists are teratogenic • Bosentan use requires two separate methods of contraception.	• Non-estrogen containing formulations are best • Barrier methods may be effective	• Prevention of pregnancy and associated morbidity/mortality		**COR I** **LOE C**

Table S5. COR, class of recommendation; LOE, level of evidence. COR and LOE grading (higher than COR IIb and LOE C) is based on pediatric study data, adult RCTs that included > 10% children, and studies on adults on congenital heart disease (ACHD).

Table S6a. Potential Drug Interactions with PAH-targeted Pharmacotherapy

PAH drug	Mechanism of Interaction	Interacting drug	Interaction
Ambrisentan	CYP3A4 substrate	Cyclosporine Ketoconazole	Caution is required in the co-administration of ambrisentan with ketoconazole and cyclosporine. Clarithromycin increased AUC of ambrisentan by +41 % and C_{max} by +27 %
Bosentan	CYP3A4 inducer. Inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine	Sildenafil	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug, but signs of increased bosentan effects should be monitored.
	CYP3A4 substrate	Cyclosporine	Cyclosporine levels fall 50%; bosentan levels increase 4-fold. Combination contra-indicated
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course, but signs of increased bosentan effects should be monitored.
	CYP3A4 substrate	Ketoconazole Itraconazol Ritonavir	Bosentan levels increase 2-fold, so that a drug combination is not recommended.
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of glibenclamide. Combination contra-indicated
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels increase considerably. Combination contraindicate
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain
	CYP2C9 inducer	HMG CoA Reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored
	CYP2C9 inducer and CYP3A4 inducer	Warfarin	Increases warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary
	CYP3A4 inducer and CYP2C9 inducer	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable
Macitentan	CYP3A4 substrate	strong CYP3A4 inhibitor Ketoconazol Itraconazol Voriconazol Claritrhromycin Telitrhomycin Nefazodon Ritonavir Saquinavir	2-fold increase of Macitentan A combination of these medications should be handled with caution(6) or be avoided.
	CYP3A4 substrate	strong CYP3A4 inducer: Rifampicin St John's wort Carbamazepin Phenytoin	reduced efficacy of Macitentan should be considered, combination should be avoided(7, 8)
	CYP3A4 substrate,	Combined CYP3A4 and OATP inhibitor: Cyclosporin	No clinically relevant interaction(7)
	CYP2C9 and CYP3A4	CYP2C9 and CYP3A4 substrate: S-/R-Warfarin	No clinically relevant interaction(7)
	CYP2C9 and CYP3A4	CYP2C9 and CYP3A4 substrate: S-/R-Warfarin	No interaction, no dose adjustment(9)
	CYP3A4 substrate	CYP3A4 substrate: Sildenafil Rivaroxaban	No interaction(8)
	CYP3A4 substrate	CYP3A4 substrate: contraceptives	No interaction(10)

Table S6b. Potential Drug Interactions with PAH-targeted Pharmacotherapy (continued)

PAH drug	Mechanism of Interaction	Interacting drug	Interaction
Selexipag	CYP2C8 substrate	moderate CYP2C8 inhibitor Clopidogrel Deferasirox Teriflunomid	Limited data. Selexipag and active metabolit could potentially increase. Consider dose adjustment of selexipag. Follow-up unpublished study on clopidogrel (NCT03496506).
	CYP2C8 substrate	Strong CYP2C8 inhibitor Gemfibrozil	Combination contraindicated Exposure to selexipag 2-fold increased, active metabolite 11-fold increased(11)
	CYP2C8 substrate	CYP2C8 inducers Rifampicin	active metabolite of selexipag reduced 50 %, consider dose adjustment
	CYP2C8 substrate	CYP2C8 inducers Carbamazepin Phenytoin	No data Active metabolite could be reduced, consider dose adjustment
	CYP3A4 substrate	Strong CYP3A4 inhibitor Lopinavir/Ritonavir	Selexipag increased 50 %, active metabolite unchanged. As active metabolite is 37fold stronger, no clinical relevance of interaction (CYP3A4 pathway seems of no clinical relevance)
	CYP3A4 substrate	CYP3A4 substrate Midazolam	No dose adjustment (CYP3A4 pathway seems of no clinical relevance)
	CYP3A4 substrate	CYP3A4 substrate Hormonal contraceptives	No data, no interaction, as contraceptives are CYP3A4 substrates (see Midazolam) and CYP2C9 substrates (see S-Warfarin)
	UGT1A3 und UGT2B7 glucuronidation	Inhibitors of UGT1A3 and UGT2B7 Valproat Probenecid Fluconazol	No data potential interaction with strong inhibitors cannot be excluded
	CYP2C9 substrate and CYP3A4 substrate	CYP2C9 substrate: (S-Warfarin): Warfarin CYP3A4 substrate (R-Warfarin): Warfarin	No interaction, no dose adjustment of Warfarin or Selexipag necessary(12)
Sildenafil (13)	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug
	CYP3A4 substrate	HMG CoA reductase inhibitors	May increase simvastatin/atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinovir increase sildenafil levels markedly
	CYP3A4 inducer	Phenytoin	Sildenafil level may fall
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase. May not require dose adjustment for a short course
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment
	cGMP	Nitrates Nicorandil Molsidomine	Profound systemic hypotension, combination contraindicated
Tadalafil (14)	CYP3A4 substrate	Bosentan	Tadalafil exposure decreases by 42%, no significant changes in bosentan levels(15). May not require dose adjustment
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contraindicated

Legend under Table 6c.

Table S6c. Potential Drug Interactions with PAH-targeted Pharmacotherapy (continued)

PAH drug	Mechanism of Interaction	Interacting drug	Interaction
Riociguat (16, 17)	Stimulation of cGMP production and inhibition of cGMP degradation	Sildenafil, Tadalafil, Vardenafil	Hypotension, combination contraindicated, Washout of 24h for sildenafil and 48 h for tadalafil possible (US-Label)
	Stimulation of cGMP production and inhibition of cGMP degradation	Nitrates Nicorandil	Hypotension, combination contraindicated,
	Stimulation of CYP 3A4 and increased degradation	Bosentan	Riociguat AUC reduced by 27% without effect on 6MWD
	Alteration of gastric pH affects riociguat absorption	Antacid (Maalox)	Coadministration of aluminum hydroxide/magnesium hydroxide (Maalox_; 10 mL) reduced riociguat AUC by - 34%.. Antacids should be taken at least 2 h before or 1 h after riociguat. Further riociguat dose adjustment beyond the individual dose-adjustment scheme is not necessary
	Alteration of gastric pH affects riociguat absorption	Omeprazole	Pre- and coadministration of omeprazole (40 mg per day) reduced riociguat AUC by - 26%. Further riociguat dose adjustment beyond the individual dose-adjustment scheme is not necessary
	Alteration of gastric pH affects riociguat absorption	Ranitidine	Coadministration of ranitidine (150 mg qd) reduced riociguat AUC by approximately - 10%. Further riociguat dose adjustment beyond the individual dose-adjustment scheme is not necessary
	CYP3A4 inhibition and e P-gp inhibition	Ketoconazole	Pre- and coadministration of ketoconazole (400 mg qd) increased riociguat AUC by approximately +150% (Cmax increased by approximately +46%). Concomitant use of riociguat with strong multipathway CYP and P-gp/BCRP inhibitors, such as ketoconazole and HIV protease inhibitors, should be approached with caution
	CYP3A4 inhibition and e P-gp inhibition	Clarithromycin	Pre- and coadministration of clarithromycin (500 mg bid) increased riociguat AUC? by + 41% (Cmax was unchanged). Further dose adjustment beyond the individual dose adjustment scheme is not necessary for patients receiving comedication inhibiting either the CYP3A4 pathway (e.g. clarithromycin) or the P-gp/BCRP-mediated excretion of riociguat

Table S6a-c. cGMP: cyclic guanosine monophosphate. Please note that most of the listed RCT data is derived from studies in adults with PAH. Healthcare providers must obtain valid information on the approval of any of the listed medications for use in pediatric PAH in the according country. Please be aware that only the unilateral effects of "interacting drug" (3rd column) on the PAH drug (left column) and related adverse effects are listed. This table most likely does not indicate all possible drug-drug-interaction and adverse effects, so that health care providers should always consult their local pharmacy service. This table is adapted from National Pulmonary Hypertension Centres of the UK and Ireland. Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in the UK and Ireland. Heart 2008;94(suppl I):i1–41(18) and Hansmann G, Apitz C. Treatment Options for Children with Pulmonary Hypertension and Cardiac Dysfunction. Expert Consensus Statement on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension – The European Pediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102: 67-85 (19). Additional specific references are cited in the left column and can be found at the end of this supplement.

Abbreviations: Cmax, peak concentration; CYP, Cytochrom P450; HMG Coa, 3-Hydroxy-3-Methylglutaryl-Coenzym-A-Reductase; UGT, UDP-glucuronosyltransferase; cGMP, Cyclic Guanosinmonophosphate; qd, once daily; P-gp, P-glycoprotein; BCRP, Breast Cancer Resistance Protein

Table S7. Complex Congenital Heart Disease (group 5.4 PH)

Complex Congenital Heart Disease (group 5.4 PH)
Segmental pulmonary hypertension
Isolated pulmonary artery of ductal origin
Absent pulmonary artery
Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries
Hemitruncus
Other
Single ventricle
Unoperated
Operated
Scimitar syndrome

Table S7: This table on complex heart diseases specific for the paediatric age group which are associated with congenital anomalies of the pulmonary vasculature such as segmental disorders, single ventricle physiology and the scimitar syndrome. From Rosenzweig EB et al. Eur Resp J, 2018. DOI: 10.1183/13993003.01916-2018

Table S8. Congenital Post-Capillary Obstructive Lesions (group 2.4 PH)

Congenital Post-Capillary Obstructive Lesions (group 2.4 PH)
Pulmonary vein stenosis
Isolated
Associated (bronchopulmonary dysplasia, prematurity)
Cor triatriatum
Obstructed total anomalous pulmonary venous return
Mitral/aortic stenosis (including supra/subvalvular)
Coarctation of the aorta

Table S8: This table outlines the congenital post-capillary obstructive lesions most frequent in childhood. From Rosenzweig EB et al. Eur Resp J, 2018. DOI: 10.1183/13993003.01916-2018

Table S9. Persistent Pulmonary Hypertension of the Newborn (PPHN; group 1.7 PH) and Associated Disorders

Persistent Pulmonary Hypertension of the Newborn (PPHN; group 1.7 PH) and Associated Disorders	
Idiopathic PPHN	Myocardial dysfunction (asphyxia, infection)
Down syndrome	Structural cardiac diseases
Meconium aspiration syndrome	Hepatic and cerebral arteriovenous malformations
Respiratory distress syndrome	
Transient tachypnoea of the newborn	*Associations with other diseases:*
Pneumonia/sepsis	Placental dysfunction (pre-eclampsia, chorioamnionitis, maternal hypertension)
Developmental lung disease	Metabolic disease
Perinatal stress	Maternal drug use or smoking

Table S9. This table gives a summary of Persistent pulmonary hypertension of the newborn (PPHN) and associated disorders. From Rosenzweig EB et al. Eur Resp J, 2018. DOI: 10.1183/13993003.01916-2018

Table S10. Developmental Lung Disorders Associated with Pulmonary Hypertension (group 3.5 PH)

Developmental Lung Disorders Associated with Pulmonary Hypertension (group 3.5 PH)
Bronchopulmonary dysplasia
Congenital diaphragmatic hernia
Down syndrome
Alveolar capillary dysplasia with "misalignment of veins" (FOXF1)
Lung hypoplasia, acinar dysplasia
Surfactant protein abnormalities
Surfactant protein B deficiency
Surfactant protein C deficiency
ABCA3
TTF1/NKX2-1
TBX4
Pulmonary interstitial glycogenesis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

Table S10: This table provides a summary of developmental lung disorders that share the common feature of developmental vascular disturbances. From Rosenzweig EB et al. Eur Resp J, 2018. DOI: 10.1183/13993003.01916-2018

Table S11. Writing Group Disclosures: Conflicts of Interests (COI) and Relationships with Industry (RWI) of the EPPVDN Writing Group Members (2019 Updated Consensus Statement on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension)

Writing Group "2019 Updated Consensus Statement on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension. The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT"								
Category A (Chair, Co-Chair)								
Writing Group Member	**Employment**	**Research Grant (current)**	**Other Research Support**	**Speakers' Bureau/ Honoraria**	**Expert Witness**	**Ownership Interest**	**Consultant/ Advisory Board**	**Other**
Georg Hansmann (Chair)	Hannover Medical School, Germany	DFG (4348/2-2#, 4348/6-1 KFO 311#), EU (CALIPSOplus)#	None	None	None	None	None	None
Martin Köstenberger (Co-Chair)	Medical University Graz, Austria	None	None	None	None	None	Actelion*	None

Category B (WG members who have no conflicts)

Writing Group Member	Employment	Research Grant (current)	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Babar Hasan	Aga Khan University, Karatchi, Pakistan	None	None	None	None	None	None	None
R Krishna Kumar	Amrita Institute of Medical Sciences, India	None	None	None	None	None	None	None
Heiner Latus	German Heart Center, TU Munich, Germany	None	None	None	None	None	None	None
Hannes Sallmon	Charité University Medical Center Berlin, Germany	None	None	None	None	None	None	None
Dietmar Schranz	University of Gießen, Germany	None	None	None	None	None	None	None
Karin Tran-Lundmark	The Pediatric Heart Center, Lund University, Sweden	None	None	None	None	None	None	None
Gregor Warnecke	Hannover Medical School, Germany	DFG (SFB 738, KFO 311)[#], BMBF (DZL)[#]	None	None	None	None	None	None
Sven Weber	Charité University Medical Center Berlin, Germany	None	None	None	None	None	None	None

Category B (WG members who have no conflicts) - continued								
Writing Group Member	**Employment**	**Research Grant (current)**	**Other Research Support**	**Speakers' Bureau/ Honoraria**	**Expert Witness**	**Ownership Interest**	**Consultant/ Advisory Board**	**Other**
Peter Zartner	Deutsches Kinderherz-zentrum Sankt Augustin, Germany	None	None	None	None	None	None	None

Category C (WG members who have conflicts)								
Writing Group Member	**Employment**	**Research Grant (current)**	**Other Research Support**	**Speakers' Bureau/ Honoraria**	**Expert Witness**	**Ownership Interest**	**Consultant/ Advisory Board**	**Other**
Tero-Pekka Alastalo	Blueprint Genetics	None	None	None	None	Co-founder and co-owner Blueprint Genetics#	None	None
Christian Apitz	University of Ulm, Germany	None	None	Actelion*	None	None	None	None
Eric Austin	Vanderbilt University, USA	NIH R01HL134802 (Austin)#; NIH P01 HL108800 (Loyd)#, CMREF (Austin)#	Vanderbilt Institutional Funds	None	None	None	Acceleron Pharma*	None

Category C (WG members who have conflicts) - continued								
Writing Group Member	**Employment**	**Research Grant (current)**	**Other Research Support**	**Speakers' Bureau/ Honoraria**	**Expert Witness**	**Ownership Interest**	**Consultant/ Advisory Board**	**Other**
Damien Bonnet	AP-HP, University Paris Descartes, France	Fédération Française de Cardiologie Société Française de Cardiologie[#]	None	Actelion*, Pfizer*, EliLilly*, Bayer*	None	None	Actelion*, Pfizer*, EliLilly*, Bayer*	None
Werner Budts	University Hospitals Leuven and Catholic University Leuven	Catholic University Leuven EWM-D2938-C24/17/069 [#]	None	Abbott*, Occlutech*	None	None	Abbott*, Occlutech*	None
Michele D'Alto	University "L. Vanvitelli" – Monaldi Hospital, Naples, Italy	None	None	Merck Sharp & Dohme*	None	None	Actelion*, Merck Sharp & Dohme*, GlaxoSmithKline*	None
Michael Gatzoulis	Royal Brompton Hospital, London, UK	None	None	Actelion*	None	None	Actelion* GSK*	None
Rainer Kozlik-Feldmann	University Heart Center Hamburg, Germany	None	None	Actelion*	None	None	None	None
Astrid Lammers	Münster University Hospital, Germany	None	None	None	None	None	Actelion*	None

Category C (WG members who have conflicts) - continued

Writing Group Member	Employment	Research Grant (current)	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Ina Michel-Behnke	Medical University Vienna, Austria	None	None	Abbvie*	None	None	Actelion*	Venus MedTech* (DSMB)
Oliver Miera	German Heart Institute Berlin (DHZB), Germany	None	None	Actelion*	None	None	None	None
Nicholas W Morrell	Cambridge University, UK	BHF (CH/09/001/25945)#	None	None	None	Co-founder Morphogen-IX#	Actelion*, GSK*	None
Guido Pieles	Bristol Heart Institute, University of Bristol, UK	Childen with Cancer UK (No 13-160)#	None	Canon Medical Systems Ltd.*	None	None	Canon Medical Systems Ltd. *	None
Daniel Quandt	University Children's Hospital Zurich, Switzerland	None	None	None	None	None	Actelion*	None
Robert Tulloh	University of Bristol, UK	SPARKS#, 13BTL01#	NIHR Bio-medical Research Centre	Actelion, GSK, Abbvie*	None	None	Actelion, Abbvie *	None
Håkan Wåhlander	The Queen Silvia Children's Hospital, Gothenburg, Sweden	None	None	Abbvie*, Actelion*	None	None	Abbvie*, Actelion*	None

Table S11. This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives EUR 10 000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns EUR 10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.
WG members indicated their conflicts of interests (COI) and relationships (RWI) for the preceeding 5 years (January 1, 2014 – December 31, 2018).
Financial relationship: *Modest. #Significant.

SUPPLEMENTARY FIGURES

Figure S1. EPPVDN Risk Score Sheet for a Child with Pulmonary Hypertension

Patient

………………………… **Surname, First Name**	……………… **Date of Birth**	………………………… **Patient´s ID**

Parameter	Measured Variable	Lower Risk Criteria		Higher Risk Criteria	
Clinical Presentation	**Clinical evidence of RV failure** (e.g. exertional dyspnoea, fatigue, dizziness, ankle swelling, epigastric fullness and right upper abdominal discomfort or pain)	no	☐	yes	☐
	Progression of symptoms	no	☐	yes	☐
	Syncope	no	☐	yes	☐
	Growth	Normal (height, BMI)	☐	Failure to thrive	☐
	WHO functional class	*I, II	☐	*III, IV	☐
Laboratory Results	**Serum NT-proBNP**	*Minimally elevated for age or not elevated	☐	*Greatly elevated for age, i.e. >1200 pg/mL (>1yr old) Rising NT-proBNP level	☐
Medical Imaging	**Echocardiography, CMR**	Minimal RA/RV enlargement No RV systolic dysfunction RV/LV endsystolic ratio < 1 (PSAX) TAPSE normal (z > -2) S/D ratio <1.0 (TR jet) PAAT > 100 ms (>1yr old)	☐ ☐ ☐ ☐ ☐ ☐	Severe RA/RV enlargement RV systolic dysfunction RV/LV endsystolic ratio >1.5 (PSAX) TAPSE (z < -3) S/D ratio >1.4 (TR jet) PAAT <70 ms (>1yr old) Pericardial effusion	☐ ☐ ☐ ☐ ☐ ☐ ☐
Cardiac Catheterization Last CATH study (date): ………… (preceding 12 months)	**Invasive Hemodynamics**	*Cardiac index >3.0 l/min/m^2 *mRAP <10 mm Hg mPAP/mSAP <0.5 Acute vasoreactivity +	☐ ☐ ☐ ☐	*Cardiac index <2.5 l/min/m^2 *mRAP >15 mm Hg mPAP/mSAP >0.75 PVRi >15 WU x m^2	☐ ☐ ☐ ☐

Lower Risk	**Intermediate Risk**	**Higher Risk**
= at least 3 starred (*) lower-risk and no higher-risk criteria (CATH available). or = at least 5 non-starred lower-risk and no higher-risk criteria (CATH <u>not</u> available). Date:……………… ☐	= definitions of lower or higher risk not fulfilled. Date:……………. ☐	= at least 2 starred (*) higher-risk criteria including cardiac index (CATH available). or = greatly elevated NT-proBNP* and at least 5 non-starred higher-risk criteria (CATH <u>not</u> available). Date:……………. ☐

Figure S1: Pediatric Pulmonary Hypertension - Individual Risk Stratification. The above 2019 EPPVDN risk score sheet for a child with pulmonary hypertension may be used at follow-up in clinics. While serum NT-proBNP and many of the listed echocardiographic variables have normative reference values (z-scores, range) and have been validated to some extent in children with PH, this is not the case for most invasive hemodynamic criteria. Thus, the risk stratification and combination of criteria in this figure is primarily a consensus within the according task force of these guidelines. Note that changes in PAH medication and/or clinical condition often are associated with changes in hemodynamics. Only cardiac catheterization data from the preceding 12 months should be taken into account. The starred criteria (*) are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (usally within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., "6/20 lower risk score for a patient with recent cardiac catheterization data in the preceeding 12 months").
Starred criteria (*) are taken from Dardi F, Manes A, Lo Russo GV, Rinaldi A, Gotti E, Zuffa E, De Lorenzis A, Pasca F, Cassani A, Guarino D, Palazzini M, Galiè N. A pragmatic approach to risk assessment in pulmonary arterial hypertension using the ESC/ERS Guidelines, Nov 2018, Circulation. 2018;138:A15572 (abstract). The risk criteria in this figure are modified criteria from Hansmann G et al. Heart, 2016; 102: ii86–ii100(20). Abbreviations: CMRI- cardiac magnetic resonance imaging ; NT-proBNP - brain natriuretic peptide ; RV–failure - right ventricular failure ; R V – right ventricle ; RA – right atrium ; PVRI - pulmonary vascular resistance index; mPAP – mean pulmonary arterial pressure ; mRAP – mean right atrial pressure ; TR – tricuspid regurgitation**.**

Figure S2. Algorithm on Genetic Counseling and Testing for a Child with IPAH or HPAH and Family Members (EPPVDN, 2019).

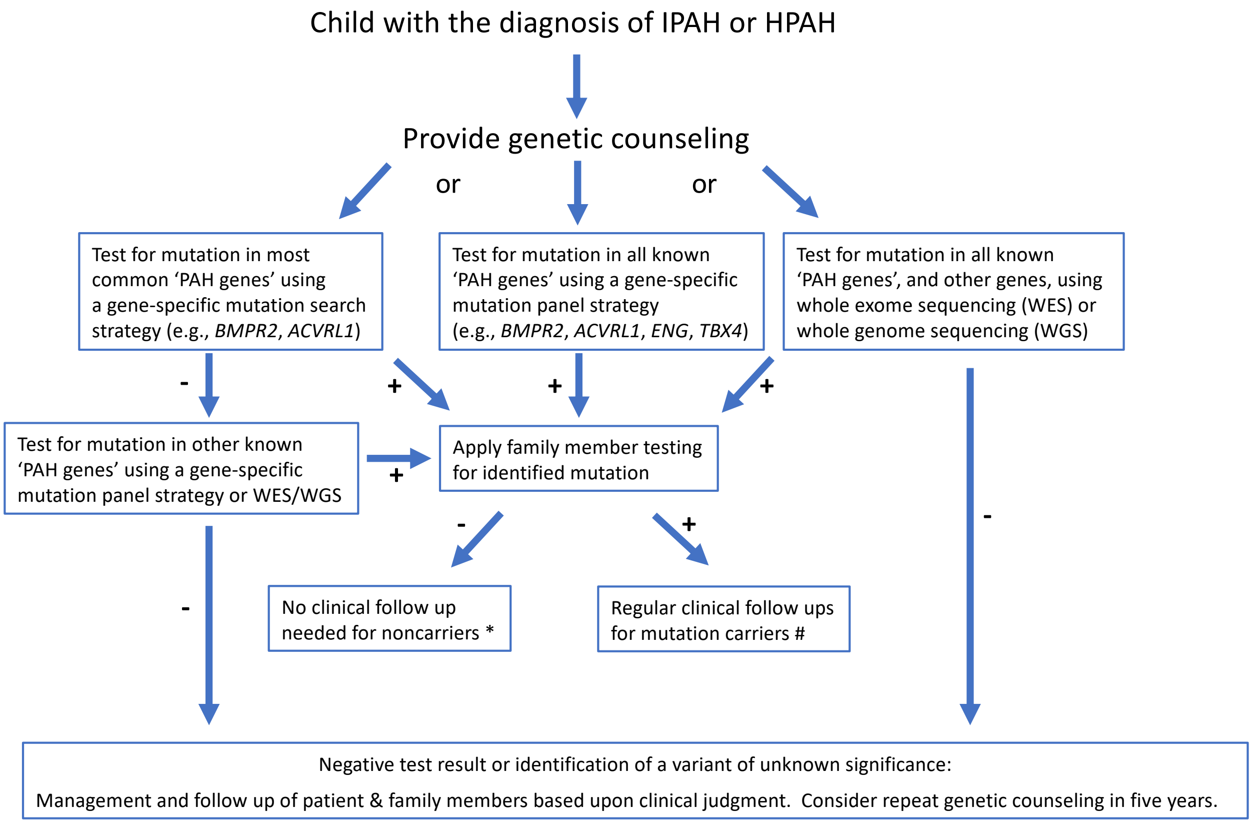

Figure S2. *Algorithm to apply genetic counseling and testing for a child with IPAH or HPAH, and family members.* (–) means negative test result; (+) means positive test result with identification of pathogenic or likely pathogenic mutation. The initial step should involve genetic counseling with the patient and his/her family. If the decision is made to pursue genetic testing, several options exist in terms of the assay used, depending on the country, financial/insurance issues, etc. These options of genetic testing include: (1) a targeted (most narrow) search of the most common genes associated with PAH; (2) a comprehensive search of all genes known to associate with PAH; or, (3) a broader assay using whole exome or whole genome sequencing. If no mutation that is pathogenic or likely pathogenic is identified which may explain the development of PAH, management and follow up of the patient and family members should be continued according to best clinical judgment with consideration of repeat genetic counseling approximatel every 5 years, as new information may be available over time. If a mutation that is pathogenic or likely pathogenic is ultimately discovered in the patient, consideration should be made for testing of first degree relatives, after additional genetic counseling is conducted. Healthy individuals who carry a genetic risk mutation should be clinically evaluated for PH every 1-3 years, with consideration for further imaging at each visit, as well.
Follow-up strategies for mutation carrier relatives have to be evaluated individually based on the age and sex of the family member, and existing family history and disease characteristics. HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; WES, whole exome sequencing; WGS, whole genome sequencing; PAH, pulmonary arterial hypertension.

Figure S3. Current Patient Registries on Pulmonary Hypertension in Middle and Low Income Regions (2019)

Figure S3. Registries on pulmonary hypertension in middle and low income regions. Pan African Pulmonary Hypertension Cohort (PAPUCO) involving 4 African countries, Pulmonary Hypertension Registry of Kerala, India (PRO-KERALA) which included 50 centers across the state of Kerala in India, Hipertension Pulmonary Asociaciones en la Argentina (HINPULSAR) included 31 centers in Argentina and Registro Colaborativo de Hipertensión Pulmonaren Argentina (RECOPILAR), a Columbian registry including 5 centers, and a prospective Ukrainian registry (adult PAH, CTEPH) from a single referral center in Kyiv, Ukraine. Overall, the majority of the patients were > 18 years of age.

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