ORIGINAL ARTICLE

Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK

Georg Hansmann, (Chair)[1] Christian Apitz, (Co-Chair)[2] Hashim Abdul-Khaliq,[3] Tero-Pekka Alastalo,[4,5] Phillip Beerbaum,[1] Damien Bonnet,[6] Karl-Otto Dubowy,[7] Matthias Gorenflo,[8] Alfred Hager,[9] Anne Hilgendorff,[10] Michael Kaestner,[2] Martin Koestenberger,[11] Juha W Koskenvuo,[4,5] Rainer Kozlik-Feldmann,[12] Titus Kuehne,[13] Astrid E Lammers,[14] Heiner Latus,[15] Ina Michel-Behnke,[16] Oliver Miera,[17] Shahin Moledina,[18] Vivek Muthurangu,[19] Joseph Pattathu,[8] Dietmar Schranz,[15] Gregor Warnecke,[20,21] Peter Zartner[22]

For numbered affiliations see end of article.

Correspondence to
Professor Dr Georg Hansmann, Department of Paediatric Cardiology and Critical Care, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany; georg.hansmann@gmail.com

This manuscript is a product of the writing group of the European Paediatric Pulmonary Vascular Disease Network (Writing Group Chair: G Hansmann, Writing Group Co-Chair: C Apitz). ISHLT, International Society of Heart and Lung Transplantation; DGPK, German Society of Paediatric Cardiology.

Received 6 December 2015
Revised 7 February 2016
Accepted 9 February 2016

ABSTRACT

The European Paediatric Pulmonary Vascular Disease (PVD) Network is a registered, non-profit organisation that strives to define and develop effective, innovative diagnostic methods and treatment options in all forms of paediatric pulmonary hypertensive vascular disease, including specific forms such as pulmonary arterial hypertension (PAH)-congenital heart disease, pulmonary hypertension (PH) associated with bronchopulmonary dysplasia, persistent PH of the newborn, and related cardiac dysfunction.

Methods The writing group members conducted searches of the PubMed/MEDLINE bibliographic database (1990–2015) and held five face-to-face meetings with votings. Clinical trials, guidelines, and reviews limited to paediatric data were searched using the terms 'pulmonary hypertension' and 5–10 other keywords, as outlined in the other nine articles of this special issue. Class of recommendation (COR) and level of evidence (LOE) were assigned based on European Society of Cardiology/American Heart Association definitions and on paediatric data only, or on adult studies that included >10% children.

Results A total of 9 original consensus articles with graded recommendations (COR/LOE) were developed, and are summarised here. The topics included diagnosis/monitoring, genetics/biomarker, cardiac catheterisation, echocardiography, cardiac magnetic resonance/chest CT, associated forms of PH, intensive care unit/ventricular assist device/lung transplantation, and treatment of paediatric PAH.

Conclusions The multipaper expert consensus statement of the European Paediatric PVD Network provides a specific, comprehensive, detailed but practical framework for the optimal clinical care of children with PH.

To cite: Hansmann G Apitz C Abdul-Khaliq H, *et al*. *Heart* 2016;**102**: ii86–ii100.

Pulmonary hypertensive vascular disease (PHVD) is a fatal disease characterised by pulmonary vascular remodelling, leading to elevated pulmonary arterial pressure, right ventricular dysfunction, left ventricular compression and consequently heart failure.[1–6] Despite significant advances in pulmonary arterial hypertension (PAH)-targeted therapies, survival of children and adults with idiopathic PAH and other forms of group 1 pulmonary hypertension (PH), such as persistent PAH after repair of congenital heart disease (CHD), remains poor.[7–12] Morbidity and mortality of paediatric PH represent substantial and growing healthcare burden:[12–15] From 1997 to 2012, shifts in case mix toward paediatric PH not associated with CHD, non-cardiac procedures and care in urban teaching hospitals have been noted in a recent retrospective study in the USA.[15] Based on a separate analysis of the period 2000–2009, the number of PH-related hospitalizations of children is increasing, and the overall mortality for PH-related hospitalizations is greater than that for hospitalizations not associated with PH (5.7% vs 0.4%; odds ratio: 16.22 (95% CI 14.8% to 17.8%), p<0.001).[16] Nevertheless, PH-associated mortality has been decreasing over the recent years in children[16 17] and adults[9 10] (box 1).

Objectives of the expert consensus statement of the European Paediatric Pulmonary Vascular Disease (PVD) Network

We were seeking to develop a framework that better defines the course of paediatric PH, identifies current gaps in our knowledge and provides a consensus statement with practical recommendation on how to best manage paediatric PH in diverse settings, acknowledging that most recommendations will have level of evidence (LOE) B or C. The 10 documents, including this executive summary, do not comprehensively review the pathobiology and clinical findings of paediatric PH, but rather contain practical recommendations for healthcare providers treating children and adolescents with different forms of PH.

Box 1 Rationale for an expert consensus statement on paediatric pulmonary hypertension

- Diagnostic and therapeutic strategies in children with pulmonary hypertension (PH) are markedly influenced by unique features of the pulmonary circulation in childhood (developmental biology) and certain paediatric diseases that are commonly associated with PH.
- A new World Symposium on Pulmonary Hypertension (WSPH) classification[18] was published in December 2013 and slightly modified in the new 2015 European Society of Cardiology European Respiratory Society guidelines on the diagnosis and treatment of PH—a document that mainly focuses on clinical care in adults.
- Yet, we felt that comprehensive, detailed but *practical* recommendations addressing the specifics of PH and pulmonary vascular disease in children are lacking.
- Recent randomized controlled trials on mono or combination PH therapy have enrolled a substantial number of children, or—more recently—have been exclusively designed to study PH in children (eg, STARTS-1, -2).
- Analyses of several paediatric patient registries (TOPP, REVEAL, COMPERA KIDS) and basic science and clinical advances have led to multiple high-impact publications in the past 10 years.
- The unique features of paediatric PH were—for the first time—recognized at the 2013 WSPH in Nice, resulting in a brief 10-page document on paediatric PH.[19] In addition, the first specific paediatric pulmonary hypertensive vascular disease classification (Pulmonary Vascular Research Institute, Panama) published in 2011[20] is currently undergoing revisions and modifications, as practicing PH doctors aim to apply the detailed paediatric-specific classification. Hence, this multipaper expert consensus statement on the paediatric PH by our network is timely indeed.

The objectives of this multipaper consensus statement were (1) to discuss the most recent classifications of PH: World Symposium, Nice, 2013; progressive post-haemorrhagic ventricular dilatation (PPHVD) pulmonary vascular resistance index Panama 2011; European Society of Cardiology (ESC)/European Respiratory Society (ERS), 2015; (2) to summarise clinical study results and their limitations, (3) to provide graded, evidence- and expert-based recommendations for the diagnosis and treatment of infants, children and adolescents with PH (including CHD/Eisenmenger syndrome), according to the grading system provided by American Heart Association (AHA) and ESC, (4) to address features specific to PH forms in childhood, (5) to define the multiple gaps in our knowledge on paediatric PH, (6) make suggestions on future trial design and (7) to discuss emerging PH therapies (safety and efficacy).

Table 2 Levels of evidence

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

LOE, as currently proposed by the European Society of Cardiology and the American Heart Association. The colour coding was used throughout the executive summary and all individual subtopic manuscripts of the 'Expert Consensus Statements on the Diagnosis and Treatment of Paediatric Pulmonary Hypertension—The European Paediatric Pulmonary Vascular Disease Network'.
LOE, level of evidence.

METHODOLOGY

The European Paediatric PVD Network

The European Paediatric PVD Network is a registered non-profit organisation 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 paediatric PHVD, including specific forms such as PAH-–CHD, PH associated with bronchopulmonary dysplasia (BPD), persistent PH of the newborn (PPHN) and related cardiac dysfunction. In order to achieve these objectives, an interdisciplinary writing group (WG) was assembled to develop a multipaper expert consensus statement that is being published in this special issue of *Heart*.

Composition of the PVD Network's WG 'Expert Consensus Statement on the Diagnosis and Treatment of Paediatric Pulmonary Hypertension'

The WG members were recruited from Austria, Germany, Finland, France and the UK. The WG consists of 23 paediatricians (with subspecialty expertise and board certifications in paediatric cardiology, critical care and/or neonatology), a clinical physiologist and a thoracic transplant surgeon. The WG started within the German Paediatric PVD Network, a newly founded WG of the German Society of Paediatric Cardiology (DGPK) in

Table 1 Classes of recommendations

Classes of recommendations	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 favour 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

Classes of recommendations, as currently proposed by the European Society of Cardiology and the American Heart Association. The colour coding was used throughout the executive summary and all individual subtopic manuscripts of the 'Expert Consensus Statements on the Diagnosis and Treatment of Paediatric Pulmonary Hypertension—The European Paediatric Pulmonary Vascular Disease Network'.

Box 2 Definitions

Pulmonary Hypertension (PH)
- mPAP ≥25 mm Hg in children >3 months of age at sea level

PAH
- mPAP ≥25 mm Hg
- PCWP <15 mm Hg
- PVR index >3 WU×m^2

Idiopathic Pulmonary Arterial Hypertension (PAH)
- PAH with no underlying disease known to be associated with PAH

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

Pulmonary hypertensive vascular disease

For biventricular circulations:
- mPAP ≥25 mm Hg and PVR index >3 WU×m^2

For circulations with cavopulmonary anastomosis (eg, Fontan physiology):
- mean TPG >6 mm Hg (calculate mPAP minus mLAP or PCWP) or PVR index >3 WU×m^2
- Detailed haemodynamic definitions of PH (eg, precapillary vs postcapillary PH, value of the diastolic transpulmonary pressure gradient) by the European Paediatric Pulmonary Vascular Disease Network are presented in ref. 23.
- mPAP, mean pulmonary artery pressure; mLAP, mean left atrial pressure; PAH, pulmonary artery hypertension; PCWP, pulmonary capillary wedge pressure (syn. PAWP, pulmonary artery wedge pressure); PVR, pulmonary vascular resistance; and TPG, transpulmonary pressure gradient; WU, Wood units.

2013, and then quickly evolved into the multinational European Paediatric PVD Network that now publishes the expert consensus statement. The majority of the 24 authors of the PVD network's WG are also members of the WG of 'PH and heart failure' of the 'Association for European Paediatric and Congenital Cardiology' (AEPC). Georg Hansmann is chair and Christian Apitz is co-chair of the according WG of the European Paediatric PVD Network.

Special features of this expert consensus statement—the multipaper approach leading to recommendations for the practicing physician and specialised PH doctor

- Conventional consensus statements or guidelines published by scientific societies tend to be >40-page documents attempting to cover all aspects of an often very heterogeneous disease, and thus may—at times—become too unwieldy to fully address the needs of the practicing healthcare providers and their patients, immediate relatives and insurance companies. WGs are usually large and—due to the time-consuming voting, writing and editing processes—very relevant original publications of the preceding 12–18 months often cannot be included in such a large document before it is published.
- We followed a *novel approach* and created small taskforces within an interdisciplinary international multiexpert WG, to develop nine individual papers by clinical topic plus this executive summary and grouped the manuscripts in a special issue entitled 'paediatric pulmonary hypertension'. All 10 papers include graded recommendations according to the grading system provided by the ESC and the AHA. All articles underwent a rigorous peer review process (see below).
- Within the multipaper concept, we divided the topics as they relate to the 'syndrome paediatric PH' by the clinical

Table 3 Recommendations on diagnosis, monitoring and outpatient care in children with suspected or confirmed PH/PPHVD[21]

Recommendations	COR	LOE
Children with suspected or confirmed PH/PPHVD should be referred to, comprehensively evaluated and treated in multidisciplinary, specialised paediatric centres.	I	C
The initial evaluation should include a comprehensive medical history, thorough physical examination, assignment to a functional class and formal assessment of cardiac function (ECG and echocardiogram). This should be followed by further diagnostic testing to delineate the PH aetiology—ideally prior to the initiation of therapy.	I	B
A CXR is recommended at baseline with acceptable risk/ radiation exposure.	I	B
Regular CXRs at follow-up are not indicated, unless there is a clinical reason.	III	B
Serial echocardiograms and ECGs are recommended every 3–6 months. In unstable or symptomatic patients or those who undergo therapeutic changes, more frequent echocardiograms may be indicated.	I	B
Further imaging is recommended to exclude underlying parenchymal lung disease, pulmonary veno-occlusive disease, CTEPH and anatomical obstructions, which may be beyond what can be diagnosed by routine transthoracic echocardiography.	I	C
If CTEPH is suspected, and a definite diagnosis is still pending despite exhaustion of other imaging modalities (cardiac catheter, chest CT), a ventilation–perfusion scan can be useful for selected patients.	IIa	C
If no underlying cause of the PH is evident, an abdominal ultrasound is indicated to rule out liver cirrhosis and/or portal hypertension.	I	C
A sleep study (polysomnography) should be performed in patients with PH at risk for sleep-disordered breathing, especially patients with Trisomy 21, other syndromes or patients with significant daytime sleepiness.	I	B
In patients with PH who are not particularly at risk for sleep-disordered breathing but have an inadequate response to PAH-targeted pharmacotherapy, a sleep study is recommended and can provide additional information.	I	B
Serial CPET (treadmill, bicycle) and the 6MWT are recommended to assess and monitor exercise tolerance, gauge prognosis and for surveillance of therapy in children with PH of an appropriate age.	I	B
Pulse oximetry during CPET/6MWT is helpful to allow shunt detection, especially in patients with PAH–CHD.	IIa	C
Blood gas analysis in paediatric patients with PH can be useful at rest, at ventilatory threshold and at maximal exercise during CPET. If available, analysis should include haemoglobin and lactate.	IIa	C
A basic lung function test (ie, body plethysmography) should be performed at the time of diagnosis, to rule out any coexisting airway disease/lung disease (obstructive, restrictive and combined), which may need to be addressed independently to targeted PH therapy.	I	C

Continued

Table 3 Continued

Recommendations	COR	LOE
In children with end-stage disease, timely referral to and discussion with a transplant centre should be sought, if lung transplantation represents a considerable option for the individual patient.	I	C
For children with PH/PPHVD undergoing surgery or other interventions requiring sedation or general anaesthesia, consultation with cardiac anaesthesia and the PH service, and appropriate postprocedure monitoring is required.	I	C
Good communication between teams, awareness of the severity of the disease, timely preparation (including 'standby' of inhaled nitric oxide) and conscious anaesthetic strategies maintaining an adequate systemic vascular resistance and adequate preload, are recommended to reduce morbidity as well as fatal events	I	C
Female adolescents with PH/PPHVD should undergo timely counselling regarding the significant maternal and foetal pregnancy risks and options for secure contraception.	I	B
Paediatric patients with PH in the high-risk category should not participate in competitive sports.	I	C
It is recommended that children with mild-to-moderate PH/PPHVD should engage in light-to-moderate aerobic activity, but be allowed to self-limit their activities as required.	I	C
Children with PH should avoid strenuous and isometric exercise, as well as dehydration.	I	C
It is recommended that children with PH should only fly on commercial aeroplanes in a stable and compensated condition.	I	C
Children with PH should undergo all recommended routine vaccinations to prevent any deteriorations due to avoidable infections.	I	C
RSV (<2 years of age), pneumococcal and influenza vaccinations should be administered in paediatric patients with PH if no contraindications exist.	I	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and are based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref.[21] Recommendations on PH diagnostics and monitoring, specifically in neonatal chronic lung disease and persistent PH of the newborn,[27] and PAH associated with congenital heart disease,,[26] are outlined in separate articles of the PVD network.
6MWT, six-minute walk test; COR, class of recommendation; CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; CXR, chest X-ray; HR-chest CT, high resolution chest CT; LOE, level of evidence; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPHVD, paediatric pulmonary hypertensive vascular disease; PVD, Pulmonary Vascular Disease; RSV, respiratory syncytial virus.

scenario they usually occur in real life, that is, general recommendations on diagnosis/monitoring;[21] specific diagnostics tools, that is, biomarker/genetics;[22] cardiac catheterisation;[23] echocardiography;[24] and cardiac magnetic resonance/CT.[25]

- Moreover, we addressed two disease-specific, complex and common patient groups separately: (1) PH/PHVD associated with CHD, including recommendations that are relevant for both children and adolescents/adults with PAH-CHD,[26] and (2) PPHN and BPD/chronic lung disease in infancy.[27]
- Finally, detailed recommendations on therapy are given in two documents: (1) treatment of acute PH in the intensive care unit, including ventricular assist device (VAD)/extracorporeal membrane oxygenation and lung transplantation (LuTx),[28] and (2) comprehensive recommendations on mid-

Table 4 Recommendations on the use of genetic testing and biomarkers in children with PH.[22]

Recommendations	COR	LOE
Genetic counselling is recommended for families with children suffering from severe genetic disorder. This includes children with IPAH or HPAH.	I	B
Families of patients with syndromes associated with PAH should be educated on the symptoms of PAH and recommended to seek clinical evaluation if the child should develop symptoms of PAH.	I	C
It is recommended to screen asymptomatic PAH mutation carriers, also children, with serial echocardiograms, and potentially other non-invasive studies	I	C
Genetic testing for PAH-associated genes such as *ACVRL1, BMPR2, CAV1, ENG and KCNK3* can be useful for children with PAH of unknown cause to allow definition of aetiology, estimation of prognosis and identification of family members at risk, and to inform family planning.	IIa	C
Genetic testing of first-degree relatives of an index patient with PAH and a known disease-causing mutation can be useful for risk stratification and rationalising surveillance.	IIa	C
Genetic testing for mutations in *EIF2AK4* gene should be considered for children with suspicion of PVOD to allow for definition of aetiology and identification of family members at risk, and to inform family planning.	IIa	C
HPAH patient's family members who develop new cardio-respiratory symptoms should be evaluated immediately for PAH	I	C
Comprehensive NGS panels targeting all known genetics in PAH can be considered to maximise diagnostic efficacy and increase cost-effectiveness in genetic diagnostics	IIb	C
Genetic testing for PAH-associated genes can be considered for patients with CHD and 'out of proportion' PAH (eg, PAH with small atrial shunt).	IIb	C
Measurement of natriuretic peptides BNP or NT-proBNP is recommended to evaluate disease severity, progression and treatment response in patients with PH.	I	B
It is uncertain whether analysis of uric acid levels can be used to evaluate disease severity	IIb	C
Analysis of circulating endothelial cells can be useful to stratify operative risk, evaluate for progression of disease and/or response to therapy in children with PAH	IIa	B

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and are based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 22.
ACVRL1 (ALK1), activin-like kinase-type 1; BMPR2, bone morphogenetic protein receptor 2; BNP, brain natriuretic peptide; CAV1, caveolin 1; CHD, congenital heart disease; COR, class of recommendation; EIF2AK4, eukaryotic translation initiation factor 2-α kinase 4; ENG, endoglin; HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; KCNK3, potassium channel subfamily K, member 3; LOE, level of evidence; NGS, next-generation sequencing; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

Table 5 Recommendations on haemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease[23]

Recommendations	COR	LOE
Cardiac catheterisation is indicated in all paediatric patients with PH to confirm diagnosis, evaluate the severity and when PH-specific drug therapy is considered.	I	C
Initial cardiac catheterisation should include right as well as left heart catheterisation to establish the diagnosis (not only RHC), if there is no contraindication.	I	C
Cardiac catheterisation may be omitted in acutely presenting, critically ill patients requiring immediate initiation of therapy	I	B
Cardiac catheterisation for the diagnosis of PAH should include AVT, unless there is a reasonable contraindication, such as PH associated with left heart disease (PH Group II)	I	C
AVT to assess prognosis and indication for specific PH therapy: The haemodynamic change that defines a positive response to AVT in PH without shunt (Qp:Qs=1:1) for children should be considered as a >20% fall in mean PAP and PVRi/SVRi ratio without a decrease in cardiac output	IIa	C
Haemodynamic indicators of PH severity are PVRi/SVRi ratio and PVRi, rather than percent fall in mean pulmonary artery pressure during AVT. Severe PH with high PVRi/SVRi ratio and high PVRi requires advanced and/or combination therapy.	IIa	C
AVT to assess operability of APAH-CHD: The haemodynamic change that defines a positive response to AVT in PH with shunt (Qp:Qs >1.5:1) for children should be considered as a >20% fall in PVRi and PVRi/SVRi with respective final values<6 iWU and <0.3.	IIa	C
Cardiac catheterisation and acute vasoreactivity testing should be performed in experienced paediatric heart centres, able to manage potential complications such as PH crisis, potentially requiring extracorporeal membrane oxygenation (depending on disease severity).	I	C
The patient's level of consciousness during cardiac catheterisation should be consistent in subsequent invasive assessments.	I	C
The preferred mode to perform cardiac catheterisation in a patient PH/PPHVD who is spontaneously breathing, either awake or moderately sedated.	I	C
Vasoreactivity testing should be performed using nitric oxide as vasodilator.	I	C
Vasoreactivity testing with the initial combination of nitric oxide and oxygen is reasonable and shortens the AVT study.	IIa	C
The use of calcium channel blocker, intravenous epoprostenol or intravenous adenosine in acute vasoreactivity testing is not recommended in children and may cause harm.	III harm	C
Repeat cardiac catheterisation should be considered in case of clinical deterioration for assessment of treatment effect, detection of early disease progression, listing for lung transplant in children with PH/PPHVD/PAH.	IIa	C
Intervals for repeat catheterisations should be based on clinical judgement but include worsening clinical course, significant change in pharmacotherapy (eg, drug class), or failure to improve during treatment	I	C
It may be reasonable to have a stable patient with PH/PPHVD on combination therapy (>one medication) undergoing cardiac catheterisation every 12–24 months	IIb	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association, and are based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 23. AVT, acute vasoreactivity testing; CHD, congenital heart disease; COR, class of recommendation; LOE, level of evidence; PAP, pulmonary artery pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPHVD, paediatric pulmonary hypertensive vascular disease; PVRi, indexed pulmonary vascular resistance; RHC, right heart catheterisation; SVRi, indexed systemic vascular resistance.

Table 6 Recommendation on transthoracic echocardiography (TTE) in paediatric pulmonary hypertension[24]

Recommendations	COR	LOE
1. Following the initial diagnostic evaluation for PH, TTE should be performed at 3–6 month intervals or earlier when the clinical condition or medication changes	I	C
2. A TTE study of a child with a suspected PH should include the assessment of the following variables:		
2.1. Estimation of the systolic PAP, by estimating RVSP through the measurement of the velocity of the TR jet by CW Doppler	I	B
2.2. Estimation of mean PAP and end-diastolic PAP through CW Doppler of pulmonary regurgitation jet	IIa	C
2.3. RV longitudinal systolic function (tricuspid annular plane systolic excursion)	I	B
2.4. RV strain and strain rate measurements	IIb	C
2.5. RV volumes by three-dimensional echocardiography	IIb	C
2.6. RV systolic to diastolic duration ratio (CW Doppler, TR jet)	IIb	C
2.7. Tissue Doppler velocities (LV, septal, RV)	IIa	B
2.8. RV/LV diameter ratio	IIa	C
2.9. PA acceleration time (PAAT)	IIb	C
3. The presence of a PE by TTE indicates poorer survival in adults with PH. PE develops frequently in patients with PAH. Currently, no data on the significance of PE in paediatric PH are available	IIb	C
4. RA enlargement plus interatrial septal bowing from right to left shows poor RV compliance or increased mean RA pressure in adults. Currently, no data on RA dilation in paediatric PH are available	IIb	C
5. TTE is useful method to screen for increased PAP	I	B
6. TTE can neither establish the definite diagnosis of PH nor classify PH subgroups, and is not sufficient to initiate a targeted therapy	I	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology (ESC) and the American Heart Association (AHA), and were based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 24. COR, class of recommendation; CW, continuous wave; EI, eccentricity index; LOE, level of evidence; LV, left ventricle; PAAT, pulmonary artery acceleration time; PAP, pulmonary artery pressure; PE, pericardial effusion; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PR, pulmonary regurgitation; RA, right atrium; RV, right ventricle; RVSP, right ventricular systolic pressure; S', peak systolic velocity; SR, strain rate; TAPSE; Tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Table 7 Recommendations on the use of cardiac magnetic resonance and computed tomography in children with suspected or confirmed PH/ PPHVD[25]

Recommendations	COR	LOE
cMRI without anaesthesia/sedation is recommended in children with suspected PH/PPHVD as part of the diagnostic evaluation and during follow-up to assess changes in ventricular function and chamber dimensions.	I	B
It is recommended that a cMRI study of a child with suspected PH/PPHVD should include the following modules. Cine cMRI for the assessment biventricular volume, function and mass using a stack of axial or short axis slices covering the entire heart.	I	B
A cMRI study of a child with suspected PH/PPHVD should include the following modules: Standard 2D flow (PCMRI) measurements at the MPA, RPA, LPA, AAO.	I	B
A cMRI study of a child with suspected PH/PPHVD may include the following modules: standard 2D flow (PCMRI) measurements at the pulmonary veins.	IIb	B
A cMRI study of a child with suspected PH/PPHVD may include the following modules: late gadolinium enhancement may be considered for the assessment of presence and amount of myocardial fibrosis.	IIb	C
It is uncertain whether a cMRI study of a child with suspected PH/PPHVD should include simultaneous invasive pressure measurements (cMRI guided cardiac catheterisation) to calculate PVR (combined with pulmonary flow measurements) and/or to assess load-independent indices of ventricular function (combined with ventricular flow measurements).	IIb	C
A cMRI study of a child with suspected PH/PPHVD may include the following modules: gadolinium contrast-enhanced or non-contrast-enhanced angiography to assess morphology and size of the pulmonary arteries, pulmonary arterial tree and quantify pulmonary perfusion (CE-MRI).	IIb	C
It is uncertain whether a cMRI study of a child with suspected PH/PPHVD should include the following modules: Assessment of regional RV myocardial function by cMRI tagging techniques.	IIb	C
It is uncertain whether a CMR study of a child with suspected PH/PPHVD should include the following modules: Non-invasive estimation of RV afterload variables, including RVP/PAP/PVR using different proposed cMRI techniques (interventricular septal position, flow measurements, pulmonary distensibility and elastance, RV–PA coupling).	IIb	C
High-resolution chest CT with angiography is recommended in the initial assessment of a child with suspected PH/PPHVD.	I	C
In case an obvious cause for PH/PPHVD, such as left-to-right cardiovascular shunt, a chest CT may be omitted.	IIb	C
High-resolution chest CT is indicated in every patient being evaluated for lung transplantation.	I	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association, and were based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 25. 2D, two-dimensional; AAO, ascending aorta; cMRI, cardiovascular MRI; CE-MRI, contrast-enhanced MRI; COR, class of recommendation; LOE, level of evidence; LPA, left pulmonary artery; MPA, main pulmonary artery; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PCMRI, phase-contrast MRI; PPHVD, paediatric pulmonary hypertensive vascular disease; PVR, pulmonary vascular resistance; RPA, right pulmonary artery; RVP, right ventricular pressure; RV–PA, right ventricular-pulmonary arterial.

Table 8 Recommendations on the evaluation and management of PH in children and adolescents with CHD (CHD–PAH, CHD–PPHVD)[26]

Recommendations	COR	LOE
Children/adolescents with clinically confirmed CHD should undergo specific transthoracic echocardiography (TTE) screening for PAH and/or ventricular dysfunction. TTE cannot reliably distinguish between PAH with increased PVR (PPHVD) and without elevated PVR.	I	C
In children and adolescents with PAH/PPHVD–CHD, a complete diagnostic work-up needs to be performed in order to determine whether PAH is associated or causally related to concomitant CHD.	I	C
Operability/catheter intervention: Surgery or interventional closure for CHD with simple post-tricuspid shunts (VSD, PDA) and significant left-to-right shunting should preferably be performed within the first 6 months of life.	I	C
Children with PAH–CHD and significant left-to-right shunting, congestive heart failure (pulmonary congestion), failure to thrive, and SpO2 >95% (lower extremities) can be considered "operable" for shunt closure; however, perioperative PH crisis may occur.	IIa	C
Children with PAH–CHD, significant left-to-right shunting and uncertainties regarding the PVR are recommended to undergo comprehensive right and left heart catheterisation regardless of the patient's age.	I	C
Operability: Children with CHD and simple defects (VSD, PDA) beyond the typical date of surgery (see main text) or those with shunts and cyanosis should undergo comprehensive right and left cardiac catheterisation (see CHD–PAH algorithm, figure 3).	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/surgery/percutaneous interventional device closure	I	C
Children with PVRI ≥6 WU×m^2 and a PVR/SVR-ratio ≥0.3 have to be evaluated by acute vasodilative testing.	I	C
Operability in complex CHD has to be judged individually, considering age, size and type of lesions and associated syndromes.	I	C
In children/adolescents with single ventricle physiology, the haemodynamic threshold for operability pre Fontan surgery is probably a mean TPG <6 mm Hg	IIa	C
In clinically asymptomatic children/adolescents with single ventricle physiology and total cavopulmonary connection (Fontan), a PVRI <3 WU×m^2 and mean TPG <6 mm Hg is consistent with acceptable haemodynamics.	IIa	C
Children/adolescents with total cavopulmonary connection (Fontan) signs of increased PVRI and/or low Qp and/or hepatic congestion should undergo complete diagnostic work-up, including comprehensive cardiac catheterisation.	IIa	C
In children/adolescents with total cavopulmonary connection (Fontan) and PHVD (TPG is ≥6 mm Hg), or those Fontan patients with symptoms irrespective of haemodynamics, targeted PH therapies should be considered to improve exercise capacity.	IIa	C
In inoperable children/adolescents with Eisenmenger syndrome, targeted pharmacotherapy as single drug or combination therapy (sequential, upfront) may be used, depending on WHO functional class and symptoms.	IIa	C
In inoperable children/adolescents with Eisenmenger syndrome, iron supplementation (by mouth, intravenously) may be administered if iron deficiency is present.	IIb	C
In inoperable children/adolescents with Eisenmenger syndrome, supplemental oxygen may be considered to reduce symptoms after careful examination (when PaO_2<60 mm Hg).	IIb	C
In inoperable children with Eisenmenger syndrome and neurological symptoms (headaches, TIA, stroke), phlebotomy may be indicated in severe hyperviscosity syndrome (MCV >80 fL).	IIb	C
In inoperable children/adolescents with Eisenmenger syndrome, anticoagulation may be considered in the absence of haemoptysis.	IIb	C
In children/adolescents with PAH/PPHVD–CHD and left heart congestion either due to obstruction or secondary to myocardial dysfunction, it is recommended to perform full haemodynamic evaluation by comprehensive right and left heart catheterisation.	I	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and are based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 26. CHD, congenital heart disease; COR, class of recommendation; LOE, level of evidence; MCV, mean corpuscular volume; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PPHVD, paediatric pulmonary hypertensive vascular disease; PVR, pulmonary vascular resistance; PVRI, PVR index; Qp, pulmonary blood flow; SVR, systemic vascular resistance; TIA, transient ischaemic attack; TPG, transpulmonary pressure gradient; TTE, transthoracic echocardiography; VSD, ventricular septal defect; WU, Wood units.

Table 9 Recommendations for supportive measures and pharmacotherapy in PPHN and PH associated with BPD/nCLD[27]

Recommendations	COR	LOE
For the treatment of PH in the NICU, the term or preterm newborn infant should receive oxygen, ventilatory support and/or surfactant if needed to achieve a preductal SpO_2 between 91% and 95% when PH is suspected or established; lung hyperinflation and atelectasis, or lung collapse and intermittent desaturations below 85%, or hyperoxia with preductal SpO_2 above 97% should be avoided.	I	A
In a newborn infant with acute PPHN in the first hours after birth, a pCO_2 between 45–60 mm Hg and a target pH >7.25 with lactate <5mmol/L can be considered as target values.	IIa	B
The preterm and term neonate with severe PH (PPHN) and no post-tricuspid-unrestrictive shunt (e.g., no VSD) may receive PGE1 or PGE2 to maintain ductal patency in right heart failure.	IIa	B
Intratracheal surfactant can be considered for the preterm and term neonate with PPHN and pulmonary diffusion impairment (but without congenital diaphragmatic hernia) to optimise ventilation, for example, newborn with meconium aspiration syndrome and PPHN.	IIa	B
ECMO can currently not be recommended for the preterm infant <34 0/7 gestational weeks p.m. and/or <2000 g body weight, with severe PH.	III	B
The preterm infant with respiratory failure should not receive iNO for the prevention of BPD and associated PH, if not enrolled in a rigorously conducted randomised clinical trial.	III	A
iNO is indicated for treatment of PPHN in mechanically ventilated newborns to improve oxygenation and reduce the need for ECMO (a) if PaO_2 is less than 100 mm Hg (while receiving 100% oxygen), or (b) if the oxygenation index exceeds 25.	I	A
Oral sildenafil should be considered for treatment of PPHN and PH in BPD, especially if iNO is not available.	IIa	B
Intravenous sildenafil may be considered for treatment of PH, including PPHN, in critically ill patients, especially in those with an unsatisfactory response to iNO.	IIb	B
In the neonate with PPHN or BPD, intravenous prostanoids through a dedicated central line or inhaled iloprost can be beneficial.	IIa	B
Treatment of severe PPHN may be extended to ECMO if other intensive care measures fail (http://www.elso.org).	IIa	B
In infants with severe BPD with or without PH, treatment with diuretics, that is, hydrochlorothiazide and spironolactone, can be considered as long as cardiac preload is adequate.	IIa	B
All infants with proven or suspected PH should receive close follow-up, including preductal/postductal SpO2 measurements, echocardiography (1/week initially, then 1–2/month), and laboratory work-up depending on disease severity including NT-proBNP, BNP, troponin optional, guided by clinical improvement or lack thereof.	I	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and are based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 27.
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 fragment of pro-brain natriuretic peptide; PGE, prostaglandin E; PPHN, persistent pulmonary hypertension of the newborn; PH, pulmonary hypertension; VSD, ventricular septal defect.

to long-term treatment of PH/PHVD in the inpatient and outpatient setting, including pharmacotherapy, catheter interventions and surgery.[29]

Literature search, grading system of recommendations, voting and review process

Literature search

Computerized searches of the PubMed/MEDLINE bibliographic database were conducted for the time period 1990–2015. Clinical trials, guidelines, and reviews limited to paediatric data were searched using the terms 'pulmonary hypertension' *and* 5–10 other keywords, as outlined in each of the 10 articles of this special issue 'Expert Consensus Statement on the Diagnosis and Treatment of Paediatric Pulmonary Hypertension'. The primary focus of this manuscript is on group 1 PH, according to the World Symposium on Pulmonary Hypertension (WSPH) classification (Nice, 2013)[18] that was recently slightly modified in the 'ESC/ERS Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension'.[30]

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

The recommendations relate to the grading system for class of recommendation (COR) and LOE currently proposed by the ESC and the AHA (COR, table 1; LOE, table 2) and was based on paediatric data only (paediatric studies, or adult studies enrolling >10% children). The grading and voting process is described further below. Within this executive summary, only the recommendations listed in each table #1 of the 9 subtopic consensus statements are listed. A full list of references can be found in the individual 9 subtopic articles.

Table 10 Recommendations on the therapy of acute PH in the paediatric intensive care unit[28]

Recommendations	COR	LOE
Oxygen should be given when 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.	IIa	B
iNO may be considered for treatment of postoperative PH in mechanically ventilated patients to improve oxygenation and reduce the risk of pulmonary hypertensive crisis.	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.	I	B
Intravenous sildenafil may be considered for treatment of PH in critically ill patients, especially those with an unsatisfactory response to iNO.	IIb	B
Inhaled iloprost may be as effective as iNO in children with postoperative PH.	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.	IIb	C

The above recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and are based on paediatric data only (class, LOE). The complete list of references on the above subtopic can be found in ref. 28.
COR, class of recommendation; ICU, intensive care unit; iNO, inhaled nitric oxide; LOE, level of evidence; PAP, pulmonary artery pressure; PH, pulmonary hypertension.

Table 11 Recommendations on treatment of children with paediatric pulmonary hypertension[29]

Recommendations	COR	LOE
Oxygen therapy is reasonable in hypoxemic PH patients who consistently have oxygen saturations <92% or PaO_2 <60 mm Hg	IIa	C
Inhalative oxygen can be particularly useful for patients with pulmonary hypertension and an element of parenchymal lung disease (eg, bronchopulmonary dysplasia/nCLD).	IIa	B
Inhalative oxygen can be useful for patients with intrapulmonary shunt and important for patients with PH while at altitude or during air travel.	IIa	C
Based on PAH and heart failure studies in adults, *mineralcorticoid receptor blockade* with spironolactone can be beneficial in patients with PAH by improving RV and LV diastolic function, particularly in 'heart failure with preserved ejection fraction'.	IIa	C
Diuretic therapy may be considered for selected paediatric patients with pulmonary hypertension.	IIb	C
Diuretic therapy should be initiated *cautiously* since patients with PH/PPHVD are often pre-load dependent to maintain an optimal cardiac output.	I	C
The benefit of *chronic anticoagulation* (warfarin, phenprocoumon) in children with PAH is unclear (so far not studied in children).	IIb	C
Chronic anticoagulation can be useful in patients with progressive IPAH/HPAH (empirical goal INR 2.0–2.5), patients with chronic thromboembolic pulmonary hypertension, patients with low cardiac output and those with hypercoagulable states.	IIa	C
Indication for anticoagulation should be critically reviewed, especially in small children prone to haemorrhagic complications. In these cases, antiplatelet therapy (eg, ASA) may be an alternative.	IIb	C
Anticoagulation is potentially harmful in children with hereditary haemorrhagic telangiectasia or porto-pulmonary hypertension.	III harm	C
Before starting targeted PAH therapy for chronic PH/PPHVD, vasodilator responsiveness should be determined by cardiac catheterisation and anatomic obstruction from pulmonary venous disease or from left-sided heart disease should be excluded.	I	B
CCB: A trial of CCB monotherapy should be pursued only in those patients who have previously been shown to be acutely reactive to iNO±oxygen, that is, those who have a positive acute vasoreactivity response ('AVT responders').	IIa	C
For children with a negative acute vasoreactivity response or those with a failed or non-sustained response to CCBs, risk stratification should probably determine additional targeted therapy.	IIa	C
CCB are contraindicated in children who have not undergone AVT, non-responders to AVT, and those with right heart failure, that is, WHO functional class IV, regardless of acute vasodilatory response (due to potential negative inotropic effect of CCB, especially in patients with low cardiac output).	III harm	C
The majority of children with severe PAH are non-responsive to acute vasodilator testing to iNO±oxygen, and require 'targeted' therapy other than CCB.	I	C
In a child with mild-to-moderate chronic PH/PPHVD and lower risk (figure 1), initiation of *oral goal-targeted therapy* is recommended (figures 2 and 3), regardless of a negative acute vasoreactivity response and should begin with either a PDE5-inhibitor or an endothelin receptor antagonist.	I	B
Oral *sildenafil* can be useful in the setting of iNO therapy withdrawal in post-operative PH, or in the presence of PH related to chronic lung disease.	IIa	B
High-dose oral sildenafil treatment (defined in the STARTS-1/-2 RCT, and table 2), either as monotherapy or add-on drug, carries an unfavourable risk-to-benefit ratio in children (>8 kg, >1-year-old) with PAH/PPHVD, including potentially increased mortality.	III harm	B
Intravenous sildenafil can be advantageous in neonates with PPHN treated with or without iNO.	IIa	C
In severe (WHO functional class IV) and/or rapidly progressive PAH/PPHVD (diagnosed by cardiac catheterisation and non-invasive imaging), continuous intravenous *prostacyclin analogue therapy*, that is, epoprostenol or treprostinil, should be started without delay (start with prostanoid monotherapy or dual/triple combination therapy including prostacyclin analogues).	I	C
Start of prostacyclin analogue therapy with intravenous treprostinil (COR IIa, C) or intravenous iloprost treprostinil (COR IIa, C) instead of epoprostenol may be considered in certain circumstances, given the advantage of longer plasma half-life and greater stability/ease of application for both treprostinil and iloprost.	IIa	C
Early combination therapy with two oral PAH drugs in newly diagnosed (treatment naïve) children with PAH in WHO functional class II–III may be considered	IIb	C
Combination of intravenous (eg, epoprostenol, treprostinil intravenously) or subcutaneous prostacyclin analogues (treprostinil intravenously) with one or two oral PAH-targeted drugs (eg, sildenafil, bosentan) may result in better long-term survival in PAH.	IIb	C
iNO is mainly used in the intensive care unit 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.	I	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.	I	B
Atrial septostomy can 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.	IIb	C
Based on a small series of children with end-stage PAH, a surgical anastomosis between the left pulmonary artery and the descending aorta (*Potts shunt*) may be considered be a valuable alternative (destination therapy) or bridge to bilateral lung transplantation in selected cases.	IIb	C

The recommendations of the *European Paediatric Pulmonary Vascular Disease Network* relate to the grading system currently suggested by the European Society of Cardiology and the American Heart Association and are based on paediatric data only (class, level of evidence). The complete list of references on the above subtopic can be found in ref. 29. Recommendations on PH therapy, specifically in neonatal chronic lung disease and PPHN,[27] and PAH associated with congenital heart disease,[26] and the recommendations on acute PH in the intensive care unit,[28] are outlined in the according subtopic articles of this expert consensus statement.
AVT, acute vasodilator testing; CCB, calcium channel blocker; COR, class of recommendation; HPAH, hereditary pulmonary hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; LOE, level of evidence; LPA, left pulmonary artery; LV, left ventricle; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PPHVD, paediatric pulmonary hypertensive vascular disease; RCT, randomised controlled trial; RV, right ventricle.

Importantly, healthcare providers must adhere to the medication labelling and follow future drug recommendations/warnings potentially published by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) when transforming these recommendations into clinical practice.

Voting process

The WG held five face-to-face meetings to discuss the individual topics and conduct the voting on the wording of the recommendations and the grading (COR, LOE) thereof (tables 1 and 2). The according meetings were conducted on 28 January 2014 in Bad Nauheim, Germany; on 28 July 2014 in Hannover,

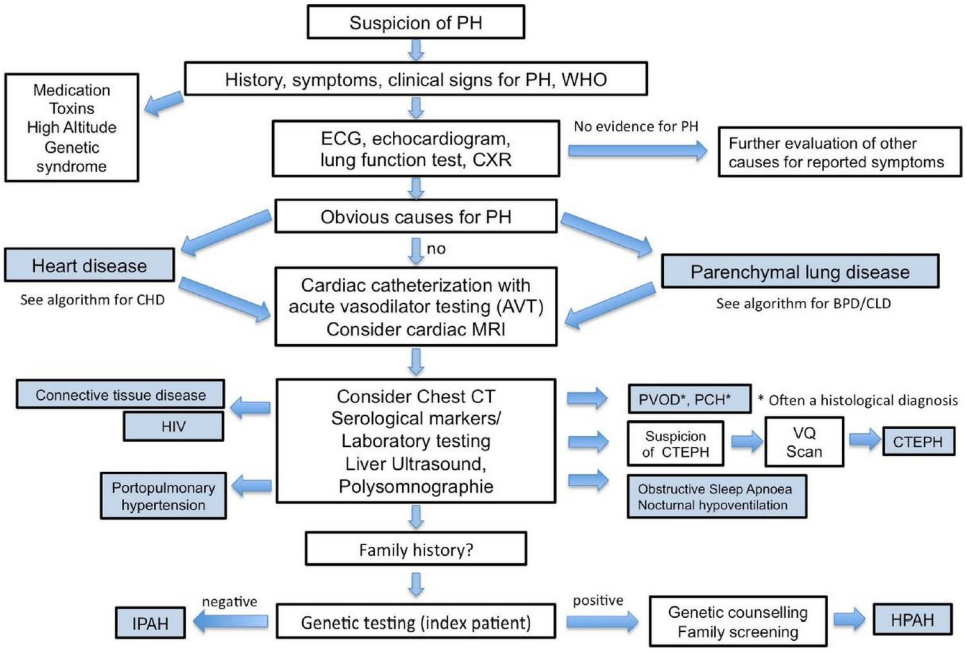

Figure 1 Diagnostic algorithm for a child or adolescent with suspected pulmonary hypertension. BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; CXR, chest X-ray; HPAH, hereditary pulmonary arterial hypertension;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

Germany; on 4 October 2014 in Weimar, Germany; on 21 May 2015 in Prague, Czech Republic; and on 6 June 2015 in Weimar, Germany. Of the 144 graded recommendations, 65 were class (COR) I, 72 were class II (39 COR IIa, 33 COR IIb); and 7 determined as class III (COR III, no benefit or harm). Three recommendations were LOE A, 41 were LOE B and the majority, that is, 100, were stratified as LOE C, due to the lack of randomized controlled studies.

Paediatric Determinants of Risk in PHVD

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I,II	WHO functional class	III,IV
Minimally elevated	Serum BNP/ NT-proBNP	Significantly elevated Rising level
	Echocardiography	Severe RV enlargement/ RV dysfunction Pericardial effusion
CI >3.0 l/min/m2 mPAP/mSAP <0.5 Acute vasoreactivity	Hemodynamics	CI <2.5l/min/m2 mPAP/mSAP >0.75 mRAP >15 mm Hg PVRi >15 WU x m2

Figure 2 Determinants of risk in paediatric pulmonary hypertensive vascular disease. The variables listed distinguish between lower and higher risk. The intermediate risk group is broad and not specifically defined. Overall, these determinants have only level of evidence C due to sparse or lack of paediatric data. Healthcare providers may include here PVR/SVR ratio, the 6 min walk distance and the max. oxygen consumption (VO_2 max.) 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. BNP, brain natriuretic peptide; CI, cardiac index (syn. Qs); IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure, mRAP, mean right atrial pressure; NT-proBNP, N terminal pro BNP; PVRi, pulmonary vascular resistance index; RA, right atrium; RV, right ventricle; SVRi, systemic vascular resistance index; WHO, World Health Organisation. Modified from McLaughlin and McGoon.[31]

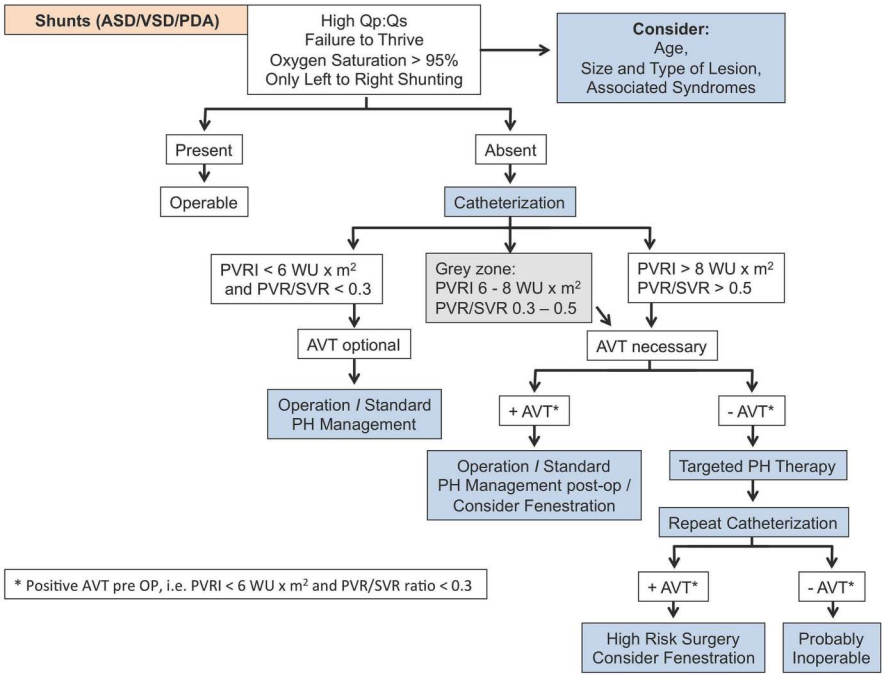

Figure 3 Algorithm for management of patients with congenital heart disease associated with PAH/PPVD and congenital shunt lesions. The indication for invasive diagnostics and eligibility for surgery/operability by comprehensive right and left heart catheterisation includes basic evaluation and AVT, the latter especially in the grey zone of forecast uncertainty. Modified from: Lopes AA and Barst R and the PVRI PAH-CHD taskforce (PVRI website; published on 26 September 2013). ASD, atrial septal defect; AVT, acute vasodilative testing; CHD, congenital heart disease; PDA, patent ductus arteriosus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; pre OP, preoperatively; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; Qp, pulmonary blood flow; Qs, systemic blood flow; SVR, systemic vascular resistance; WU, Wood units; VSD, ventricular septal defect PAH, pulmonary arterial hypertension.

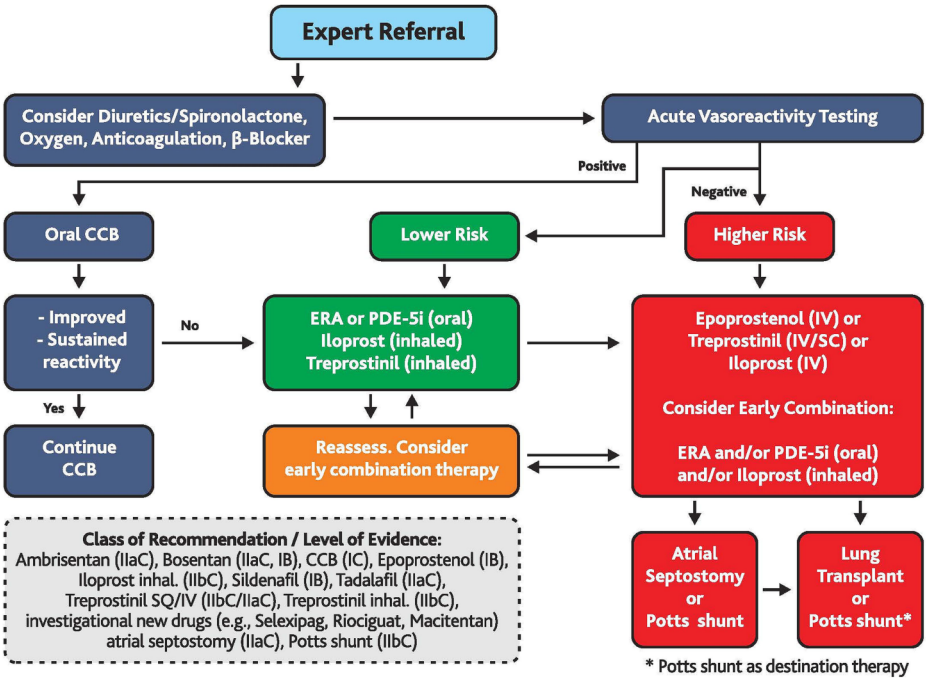

Figure 4 Treatment algorithm for paediatric pulmonary arterial hypertension. This algorithm applies to IPAH HPAH (FPAH). Solid clinical data on the therapy of other forms of PH is limited. The 'intermediate' risk group is broad and not specifically defined (see figure 1). Healthcare providers may consider upfront, early or rapid sequence-targeted PAH therapy in 'intermediate' risk group (between 'lower risk' and 'higher risk' in figure 1: 'Determinants of risk'). Use of all agents is considered off-label in children aside from sildenafil and bosentan (>1-year-old) 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 Eisenmenger syndrome, and COR IIa, LOE C for children with PAH without Eisenmenger syndrome. CCB, calcium channel blocker; COR, class of recommendation; ERA, endothelin receptor antagonist; EMA, European Medicines Agency; HPAH, hereditary pulmonary arterial hypertension; inh., inhalation; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LOE, level of evidence; PDE-5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension;; PAH, pulmonary arterial hypertension; SC, subcutaneous. Modified and expanded from Ivy *et al*.[19]

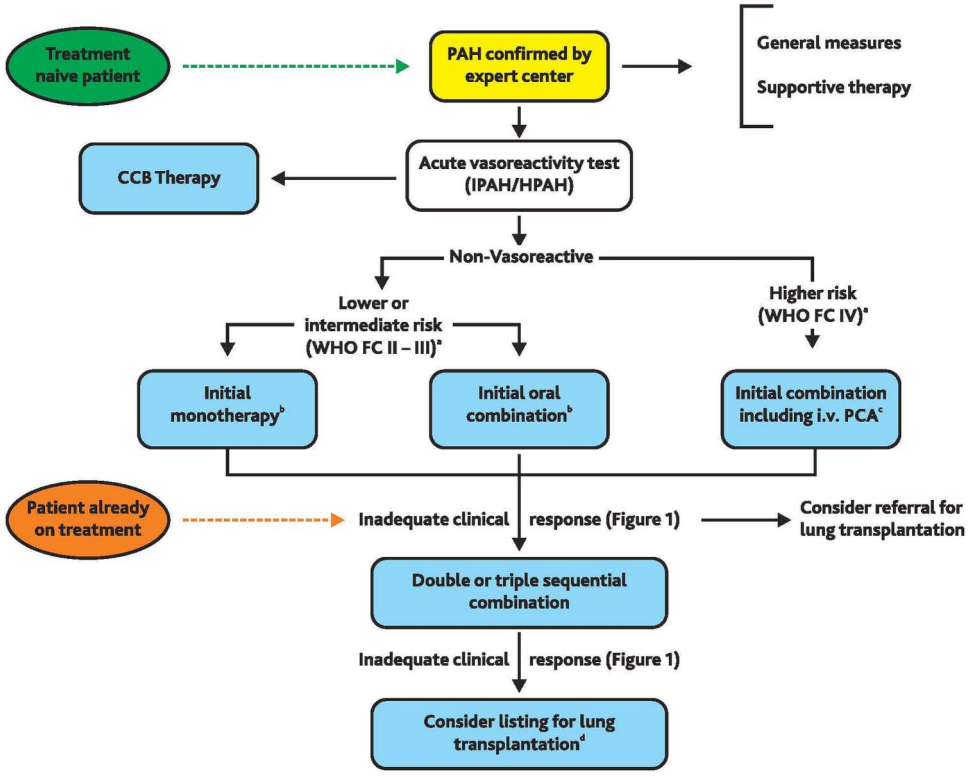

Figure 5 Treatment algorithm for combination therapy in PAH (evidenced-based only for adults with PAH, ie, group 1 PH). Bosentan received the following dual grading: COR I, LOE B for children with PAH and Eisenmenger syndrome, and COR IIa, LOE C for children with PAH without Eisenmenger syndrome. The 'intermediate' risk group is broad and not specifically defined (see figure 1). (a) Some WHO-FC III patients may be considered high risk (see table 1). (b) In adult PAH, initial combination with ambrisentan plus tadalafil has been shown to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. (c) Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high-risk adult PAH patients also as monotherapy. (d) Consider also balloon atrial septostomy. Modified from Galie *et al*.[30] CCB, calcium channel blockers; COR, class of recommendation; DPAH, drug-induced PAH; HPAH, heritable PAH; IPAH, idiopathic PAH; i.v., intravenous; LOE, level of evidence (according to European Society of Cardiology and American Heart Association). PAH, pulmonary arterial hypertension; PCA, prostacyclin analogues; WHO-FC, WHO functional class.

Peer review process

Each manuscript of the multipaper expert consensus statement has been peer reviewed by at least two anonymous external experts according the journal's standardised review process for original articles and—in addition—by two anonymous experts selected by the International Society of Heart and Lung Transplantation (ISHLT) scientific board.

Endorsement process (ISHLT, DGPK)

The ISHLT was actively involved in the peer review process as outlined above and endorsed the first five manuscripts on 3 September 2015 and the final five manuscripts on February 9, 2016. The DGPK, that is, the society for paediatric and congenital cardiology in Austria, Germany and Switzerland, endorsed the multipaper expert consensus statement on January 7, 2015 (box 2).

Summary of graded recommendations (COR, LOE) by clinical topic

See tables 3–11 and figures 1–5 for summary of graded recommendations.

Limitations of the multipaper expert consensus statement on paediatric PH

We acknowledge that most LOE of our recommendations on paediatric PH, are B or C, since only very few randomised controlled trials have been conducted so far due the heterogeneity of what is still considered a rare—but underdiagnosed—disease in the so-called developed world. Thus, we called this special issue 'Expert Consensus Statement' rather than 'Guidelines'. We

Box 3 Challenges and future directions of the European Paediatric Pulmonary Vascular Disease Network

- Identification of valid treatment goals in paediatric PAH.[6 32–35]
- Regulatory requirements, patient recruitment and retention, clinical trial endpoints for paediatric PAH trials.[33 34]
- Need to conduct multicentre studies and establish new registries for paediatric pulmonary hypertension.[14 34]
- Initiation of a prospective multicentre study on early combination therapy in paediatric including a comparative group (early combined dual or triple combination, rapid sequence of two agents).
- When and how to perform a Potts shunt procedure[36] (surgery, intervention?) for advanced PAH and how to combine this pressure-unloading shunt with combination pharmacotherapy?
- Initiation of investigator-initiated pilot and/or industry-sponsored phase 2/3 studies on the safety and efficacy of new compounds recently published/approved for adult PAH (macitentan, riociguat, selexipag, treprostinil).[29]

Table 12 Writing group disclosures: conflicts of interests and relationships with industry

WG 'expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension'

WG member	Employment	Research grant (current)	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Category A (chair, co-chair)								
Georg Hansmann (Chair of WG)	Hannover Medical School, Germany	DFG (4348/2-1)*, Fördergemeinschaft deutsche Kinderherzzentren (W-H-001/2014)*, Stiftung KinderHerz (2511-6-13-011)*	None	None	None	None	None	None
Christian Apitz (Co-Chair of WG)	University of Ulm, Germany	Behring-Röntgen-Stiftung (59-0018)*, Stiftung KinderHerz (2511-10-13-001)*	None	None	None	None	None	None
Category B (WG members who have no conflicts)								
Philipp Beerbaum	Hannover Medical School, Germany	None	None	None	None	None	None	None
Anne Hilgendorff	Ludwig-Maximilians University Giessen	Helmholtz (BMBF)*, DZL (BMBF)*	None	None	None	None	None	None
Michael Kaestner	University of Ulm, Germany	None	None	None	None	None	None	None
Rainer Kozlik-Feldmann	University Heart Center Hamburg, Germany	None	None	None	None	None	None	None
Titus Kuehne	German Heart Center Berlin (DHZB), Germany	DFG (KU1329/10-2)*, BMBF Sysmed2-012*, EU FP7* (Cardioproof, Paedigree)	None	None	None	None	None	None
Heiner Latus	University of Gießen, Germany	German Society of Paediatric Cardiology†	None	None	None	None	None	None
Ina Michel-Behnke	Medical University Vienna	None	None	None	None	None	None	None
Joseph Pattathu	University of Heidelberg, Germany	None	None	None	None	None	None	None
Dietmar Schranz	University of Gießen, Germany	Behring-Röntgen-Stiftung*, Deutsche Herzstiftung*	None	None	None	None	None	None
Gregor Warnecke	Hannover Medical School, Germany	DFG (SFB 738), DZL (BMBF)	None	None	None	None	None	None
Peter Zartner	Deutsches Kinderherz-zentrum, Sankt Augustin, Germany	None	None	None	None	None	European Society of Cardiology	none
Category C (WG members who have conflicts)								
Hashim Abdul-Khaliq	Saarland University Medical Center, Germany	None	None	None	None	None	Actelion, Inc.†	None
Damien Bonnet	AP-HP, University Paris Descartes, France	Fédération Française de Cardiologie Société Française de Cardiologie	None	Actelion Pharmaceuticals, Pfizer, EliLilly, Bayer	None	None	Actelion Pharmaceuticals, Pfizer, EliLilly, Bayer	None
Tero-Pekka Alastalo	University of Helsinki; Blueprint Genetics, Finland	None	None	None	None	Co-founder and co-owner of Blueprint Genetics*	None	None
Karl-Otto Dubowy	German Heart Center (HDZ), Bad Oeynhausen, Germany	None	None	Actelion† Bayer Vital†	None	None	None	None
Matthias Gorenflo	University of Heidelberg, Germany	None	None	Actelion, Bayer	None	None	Actelion	None

Continued

Table 12 Continued

WG 'expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension'

WG member	Employment	Research grant (current)	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Alfred Hager	Deutsches Herzzentrum München (DHM), Germany	None	None	Actelion, Inc.† Pfizer† AOP Orphan† Pharmaceuticals† OMT GmbH† GlaxoSmithKline† Medtronic† Schiller† Abbott† Encysive†	None	Siemens† Gilead† Abbvie† Pfizer† Novartis† Lilly†	Actelion, Inc.†	None
Martin Köstenberger	Medical University Graz, Austria	None	None	Actelion, Inc.†	None	None	None	None
Juha Koskenvuo	University of Helsinki; Blueprint Genetics, Finland	None	None	None	None	Co-founder and co-owner of Blueprint Genetics*	None	None
Astrid Lammers	Münster University Hospital, Germany	Dean's office (15-002) University of Münster	None	None	None	None	Actelion, Inc.†	None
Oliver Miera	German Heart Institute Berlin (DHZB), Germany	None	None	Actelion, Inc.†, Pfizer†	None	None	None	None
Shahin Moledina	Great Ormond Street Hospital, London, UK	None	None	None	None	None	Bayer†	None
Vivek Muthurangu	University College London, UK	None	None	None	None	None	GSK†	None

This table represents the relationships of WG members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the WG are required to complete and submit. A relationship is considered to be 'significant' if (a) the person receives €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 €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.
*Significant.
†Modest.

Key messages

What is already known on this subject?

Pulmonary hypertension (PH) in neonates, infants, children and adolescents is a complex condition that may be associated with diverse cardiac, pulmonary and systemic diseases, and contributes to significant morbidity and mortality. However, current approaches to caring for paediatric patients with PH have been limited by the lack of consensus recommendations from experts in the field of paediatric PH.

What might this study add?

The European Paediatric Pulmonary Vascular Disease (PVD) Network is a registered, non-profit organisation that strives to define and develop effective, innovative diagnostic tools and treatment options in all forms of paediatric pulmonary hypertensive vascular disease (PHVD), including specific forms such as pulmonary arterial hypertension–congenital heart disease, PH associated with bronchopulmonary dysplasia, persistent PH of the newborn, and related cardiac dysfunction. In order to achieve these objectives, a multipaper expert consensus statement was developed to provide comprehensive and practical recommendations.

How might this impact on clinical practice?

This multipaper expert consensus statement of the European Paediatric PVD Network provides—for the first time—a specific, comprehensive, detailed but practical framework for the optimal clinical care of children with PH/PHVD.

do strongly feel—however—that the previous PH documents provided by adult cardiology or respiratory societies or the WSPH, while improved, do not reflect to a satisfactory extent the specific complexity of *paediatric* PHVD and hence developed this consensus statement (box 3).

CONCLUSIONS

This multipaper expert consensus statement of the European Paediatric PVD Network provides a specific, comprehensive, detailed but practical framework for the optimal clinical care for children with PH/PHVD. Additional patient registries and prospective, controlled and randomised studies on the diagnosis and treatment of PH in children are urgently needed to move on from frequently experience-based towards mostly evidence-based recommendations.

WEB LINK

- European Paediatric Pulmonary Vascular Disease Network http://www.pvdnetwork.org

Author affiliations
[1]Department of Paediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany
[2]Division of Paediatric Cardiology, Children's University Hospital Ulm, Ulm, Germany
[3]Department of Paediatric Cardiology, Saarland University Hospital, Homburg, Germany
[4]Blueprint Genetics, Biomedicum Helsinki, Helsinki, Finland
[5]Department of Paediatric Cardiology, Children's Hospital Helsinki, University of Helsinki, Helsinki, Finland
[6]Unité Médico-Chirurgicale de Cardiologie Congénital et Pédiatrique, Centre de reference Malformations Cardiaques Congénitales Complexes—M3C, Hôpital Necker Enfants Malades, APHP, Université Paris Descartes, Sorbonne Paris, Paris, France
[7]Department of Paediatric Cardiology and Congenital Heart Disease, Heart and Diabetes Centre NRW, Bad Oeynhausen, Germany
[8]Department of Paediatric Cardiology, University of Heidelberg, Heidelberg, Germany
[9]Department of Paediatric Cardiology and Congenital Heart Disease, German Heart Centre Munich and Technical University, Munich, Germany
[10]Perinatal Center Grosshadern, Dr. von Haunersches Children's Hospital, Ludwig-Maximilians-University, Munich, Germany
[11]Divison of Paediatric Cardiology, Department of Paediatrics, Medical University Graz, Graz, Austria
[12]Division of Paediatric Cardiology, University Heart Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[13]German Heart Institute Berlin (DHZB), Unit of Cardiovascular Imaging, Department of Congenital Heart Disease and Paediatric Cardiology, Berlin, Germany
[14]Department of Paediatric Cardiology, University of Münster, Münster, Germany
[15]Justus-Liebig-University Giessen, Pediatric Cardiology, Paediatric Heart Center, Giessen, Germany
[16]Paediatric Heart Center, Division of Paediatric Cardiology, University Hospital for Children and Adolescents, Medical University Vienna, Austria
[17]German Heart Institute Berlin (DHZB), Department of Congenital Heart Disease and Paediatric Cardiology, Berlin, Germany
[18]National Paediatric Pulmonary Hypertension Service UK, Great Ormond Street Hospital for Children, London, UK
[19]Cardiovascular MRI Department, Great Ormond Street Hospital for Children, London, UK
[20]Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany
[21]German Centre for Lung Research, BREATH, Hannover, Germany
[22]Department of Paediatric Cardiology, German Paediatric Heart Centre, Sankt Augustin, Germany

Acknowledgements Chair and co-chair would like to thank all writing group members for their voluntary contributions and result-driven dedication to this project. We very much appreciate the support from ISHLT and DGPK leadership, the editors and editorial board of *Heart*, as well as Lindsey Fountain and Eleanor Naylor, and the editorial staff at *BMJ Publishing*.

Contributors The contributor statement can be found in table 12.

Funding This *Heart* supplement was produced with support from an unrestricted educational grant from Actelion Pharmaceuticals Germany GmbH, Bayer Pharma AG, and Pfizer Inc. None of these organisations had any influence on the composition of the writing group or the content of the articles published in this supplement.

Competing interests The European Paediatric Pulmonary Vascular Disease Network is a registered, non-profit organisation that makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional or business interest of a member of the writing panel. Specifically, 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. All authors filled out and signed a form for disclosure of potential conflict of interests provided by the International Committee of Medical Journal Editors. Chair (GH) and co-chair (CA) of this writing group indicate no conflicts of interests or relationships with industry related to the content of this article. Comprehensive information on conflict of interests, relationships with industry, current grant support of all writing group members can be found in table 12 of this article.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1 Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. *J Clin Invest* 2012;122:4306–13.
2 Tuder RM, Archer SL, Dorfmüller P, *et al*. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D4–12.
3 Reddy S, Bernstein D. Molecular Mechanisms of Right Ventricular Failure. *Circulation* 2015;132:1734–42.
4 Haddad F, Spruijt OA, Denault AY, *et al*. Right Heart Score for Predicting Outcome in Idiopathic, Familial, or Drug- and Toxin-Associated Pulmonary Arterial Hypertension. *JACC Cardiovasc Imaging* 2015;8:627–38.
5 Haddad F, Doyle R, Murphy DJ, *et al*. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation* 2008;117:1717–31.

6 Ploegstra MJ, Roofthooft MT, Douwes JM, *et al*. Echocardiography in paediatric pulmonary arterial hypertension: early study on assessing disease severity and predicting outcome. *Cir Cardiovasc Imaging* 2015;8:e000878.
7 D'Alonzo GE, Barst RJ, Ayres SM, *et al*. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343–9.
8 Barst RJ, McGoon MD, Elliott CG, *et al*. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Circulation* 2012;125:113–22.
9 McGoon MD, Benza RL, Escribano-Subias P, *et al*. Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol* 2013;62:D51–9.
10 Benza RL, Miller DP, Barst RJ, *et al*. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest* 2012;142:448–56.
11 Diller GP, Kempny A, Alonso-Gonzalez R, *et al*. Survival Prospects and Circumstances of Death in Contemporary Adult Congenital Heart Disease Patients Under Follow-Up at a Large Tertiary Centre. *Circulation* 2015;132:2118–25.
12 Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. *Chest* 2010;137:52S–61S.
13 Berger RM, Beghetti M, Humpl T, *et al*. Clinical features of paediatric pulmonary hypertension: a registry study. *Lancet* 2012;379:537–46.
14 Hansmann G, Hoeper MM. Registries for paediatric pulmonary hypertension. *Eur Respir J* 2013;42:580–3.
15 Maxwell BG, Nies MK, Ajuba-Iwuji CC, *et al*. Trends in Hospitalization for Paediatric Pulmonary Hypertension. *Paediatrics* 2015;136:241–50.
16 Frank DB, Crystal MA, Morales DL, *et al*. Trends in paediatric pulmonary hypertension-related hospitalizations in the United States from 2000–2009. *Pulm Circ* 2015;5:339–48.
17 Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006. *Heart* 2009;95:312–17.
18 Simonneau G, Gatzoulis MA, Adatia I, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34–41.
19 Ivy DD, Abman SH, Barst RJ, *et al*. Paediatric pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D117–26.
20 Cerro MJ, Abman S, Diaz G, *et al*. A consensus approach to the classification of paediatric pulmonary hypertensive vascular disease: report from the PVRI Paediatric Taskforce, Panama 2011. *Pulm Circ* 2011;1:286–98.
21 Lammers AE, Apitz C, Zartner P, *et al*. Diagnostics, monitoring and outpatient care in children with suspected pulmonary hypertension/ paediatric pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii1–13.
22 Pattathu J, Gorenflo M, Hilgendorff A, *et al*. Genetic testing and blood biomarkers in paediatric pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii36–41.
23 Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii23–9.
24 Koestenberger M, Apitz C, Abdul-Khaliq H, *et al*. Transthoracic echocardiography for the evaluation of children and adolescents with suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii14–22.
25 Latus H, Kuehne T, Beerbaum P, *et al*. Cardiac magnetic resonance and computed tomography imaging in children with suspected or confirmed pulmonary hypertension/pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii30–5.
26 Kozlik-Feldmann R, Hansmann G, Bonnet D, *et al*. Pulmonary Hypertension in children with congenital heart disease (PAH-CHD, PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii42–8.
27 Hilgendorff A, Apitz C, Bonnet D, *et al*. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii49–56.
28 Kaestner M Schranz D, Warnecke G, *et al*. Pulmonary hypertension in the intensive care unit. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii57–66.
29 Hansmann G, Apitz C. Treatment of children with pulmonary hypertension and cardiac dysfunction. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii67–85.
30 Galie N, Humbert M, Vachiery JL, *et al*. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2015;46:903–75.
31 McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation* 2006;114:1417–31.
32 Ploegstra MJ, Douwes JM, Roofthooft MT, *et al*. Identification of treatment goals in paediatric pulmonary arterial hypertension. *Eur Respir J* 2014;44:1616–26.
33 Beghetti M, Berger RM. The challenges in paediatric pulmonary arterial hypertension. *Eur Respir Rev* 2014;23:498–504.
34 Hansmann G. Interdisciplinary networks for the treatment of childhood pulmonary vascular disease: what pulmonary hypertension doctors can learn from paediatric oncologists. *Pulm Circ* 2013;3:792–801.
35 Waxman AB, Farber HW. Using clinical trial end points to risk stratify patients with pulmonary arterial hypertension. *Circulation* 2015;132:2152–61.
36 Baruteau AE, Belli E, Boudjemline Y, *et al*. Palliative Potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: updated data from the first 24 patients. *Eur J Cardiothorac Surg* 2015;47:e105–10.