Embracing the challenges of neonatal and paediatric pulmonary hypertension

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This article discusses recent advances, ongoing challenges and distinct approaches for caring for infants and children with pulmonary arterial hypertension, as presented by the paediatric task force of the 7th World Symposium on Pulmonary Hypertension. https://bit.ly/4bSg66C

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Abstract

Paediatric pulmonary arterial hypertension (PAH) shares common features with adult disease, but is associated with several additional disorders and challenges that require unique approaches. This article discusses recent advances, ongoing challenges and distinct approaches for caring for infants and children with PAH, as presented by the paediatric task force of the 7th World Symposium on Pulmonary Hypertension. We provide updates on diagnosing, classifying, risk-stratifying and treating paediatric pulmonary hypertension (PH) and identify critical knowledge gaps. An updated risk stratification tool and treatment algorithm is provided, now also including strategies for patients with associated cardiopulmonary conditions. Treatment of paediatric PH continues to be hindered by the lack of randomised controlled clinical trials. The challenging management of children failing targeted PAH therapy is discussed, including balloon atrial septostomy, lung transplantation and pulmonary-to-systemic shunt (Potts). A novel strategy using a multimodal approach for the management of PAH associated with congenital heart diseases with borderline pulmonary vascular resistance is included. Advances in diagnosing neonatal PH, especially signs and interpretation of PH by echocardiography, are highlighted. A team approach to the rapidly changing physiology of neonatal PH is emphasised. Challenges in drug approval are discussed, particularly the challenges of designing accurate paediatric clinical trials with age-appropriate end-points and adequate enrolment.

Introduction

Pulmonary hypertension (PH) may present at all stages of life, ranging from newborns to children, adolescents and adults. PH in childhood shows similarities, but also specific differences, compared to PH in adulthood. These differences may vary with age, stage of development, and aetiology of pulmonary vascular disease. Therefore, since 2013, a dedicated paediatric task force has been added to the working groups of the World Symposium on Pulmonary Hypertension (WSPH). In this third report of the paediatric task force, new data and experience in neonatal and paediatric PH since the last WSPH in 2018 are summarised, which have led to new insights and current consensus regarding the diagnosis and treatment of these children. These include definitions and characterisation of PH in different paediatric age groups, current opportunities and challenges regarding risk stratification in children and the proposal of a new

treatment algorithm for paediatric pulmonary arterial hypertension (PAH). Current gaps in knowledge and needs for future research are identified.

Definition and classification of PH in paediatrics

The haemodynamic definition of PH as applied in infants and children beyond the first months of life continues to be the same as in adults, defined as a mean pulmonary arterial pressure (mPAP) ⩾20 mmHg at rest determined by cardiac catheterisation [1, 2]. Different approaches exist for using pulmonary vascular resistance (PVR) *versus* PVR indexed for body surface area (PVRI) in children and adults. For the definition of pre-capillary PH in infants and children, a pulmonary capillary wedge pressure <15 mmHg and an PVRI >3 Wood Units·m^2 (WU·m^2) is recommended (table 1). In contrast to adults in whom a definition of nonindexed PVR >2 WU is recommended, in children blood flows are traditionally indexed for body surface area on the assumption that systemic and pulmonary blood flows change proportionally with body size, while the transpulmonary pressure gradient does not. Since blood flow is the denominator in the equation for calculating PVR, the need for indexing PVR in children is emphasised. This leads to a definition of PVRI where a pressure difference (mmHg) is divided by indexed pulmonary blood flow (L·min^{-1}·m^{-2}) that will describe indexed PVRI in mmHg×min×L^{-1}×m^2 (mmHg·min·L^{-1}·m^2) or Wood Units×m^2 (WU·m^2). The concept of indexing allows for the comparability of physiological variables in subjects of different sizes. There is some uncertainty as at which body surface area it is best to transition from using PVRI in children to using PVR in adolescents. Current definitions suggest that in children, a body surface area of 1.5 m^2 would indicate the appropriate time to change from PVRI to PVR in the definition of pre-capillary PH. Therefore, the authors recommend the use of indexed PVR for children and advise reporting both PVR and PVRI values in the transition period from adolescent to adult.

Cardiac catheterisation remains the gold standard for evaluating and diagnosing PH in neonates, infants and children. Complication rates of cardiac catheterisation are low at highly experienced paediatric PH programmes [3, 4]; however, the balance between risks and benefits must always be carefully considered if the patient is too ill, small or vulnerable. Additional risk factors for unplanned escalation of circulatory or airway support during catheterisation include age <1 year, worse functional class, group 3 PH, prematurity and any pre-operative respiratory support [4, 5]. In preterm neonates and infants aged <3 months, the risk–benefit ratio of cardiac catheterisation may preclude its use for diagnosis. In these cases, the presence, severity and physiological factors underlying PH may be determined by echocardiography realising that in these neonates, the definition of PH is less clear, changes rapidly during the cardiorespiratory transitional period after birth, and haemodynamic and physiological characterisation of PH may be difficult. Further workup is required to confirm the presence of PAH (neonatal PH is discussed later).

In 30–50% of children with group 1 PAH, PAH is associated with congenital heart diseases (CHD), but this represents a heterogeneous patient population. Some children do not fit well into the current subclassification system for PAH-CHD [1]. A recent appraisal by the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry [6] suggested changes for children that include group A: Eisenmenger syndrome; group B: left-to-right shunt; group C: coincidental defects (the authors proposed to include all atrial septal defects (ASDs) in paediatric patients in group C, as children with an ASD of any size should not develop pulmonary vascular disease during childhood and should thus be regarded “coincidental” when PAH develops in childhood); group D continues to include corrected CHD.

TABLE 1 Haemodynamic characterisation of paediatric pulmonary hypertension (PH)

	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVRI >3 WU·m^2 (mmHg·L^{-1}·min·m^2)
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVRI ⩽3 WU·m^2 (mmHg·L^{-1}·min·m^2)
Combined pre- and post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVRI >3 WU·m^2 (mmHg·L^{-1}·min·m^2)

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVRI: indexed pulmonary vascular resistance; WU: Wood Units.

TABLE 2 Classification of congenital heart disease (CHD)-associated pulmonary arterial hypertension

Group	Condition
A	Eisenmenger syndrome
B	Left-to-right shunt: correctable not correctable
C	Coincidental defects, including all (isolated) ASDs in childhood
D	Corrected CHD
E	Without (prolonged) initial shunt, *e.g.* neonatal arterial switch operation for TGA

ASD: atrial septal defects; TGA: transposition of the great arteries.

However, an additional subclass was introduced as group E, which includes patients with CHD, who could not be categorised in groups A–D because they had never had a left-to-right shunt or had an initial shunt at birth for <1–2 weeks, such as in patients born with transposition of the great arteries and repaired as neonates. We therefore now propose a modification to the previous PAH-CHD subclassification by adding a group E (table 2); this PAH-CHD subclassification now includes five clinical groups, each requiring a specific therapeutic approach (discussed in the section on treatment). Furthermore, we defined the group of patients with complex CHD associated with pulmonary vascular diseases that do not meet the criteria for PAH (table 3) and recommended to retain these patients in group 5 of the most recent clinical classification for PH (group 5.7: complex congenital heart disease) [7].

The paediatric task force acknowledges the importance of a complete diagnostic workup of children and infants with PH to reach correct phenotyping, characterisation and classification of the underlying disease. No further modification of the previously proposed diagnostic algorithm is suggested at this time [1].

Prognostic factors in paediatric PAH

Risk assessment plays a crucial role in the current management of children with PAH. Risk assessment is used to determine the patient's risk for adverse outcome, to monitor disease progression and the child's response to treatment and with that to impact treatment decisions. At previous World Symposia, the paediatric task force has proposed tables with risk factors for paediatric PAH [1, 2]. While these tables relied heavily on expert opinion, we now propose a risk tool that is predominantly based on validated risk factors. We performed a comprehensive literature review to identify risk factors reported to be associated with outcomes in paediatric PAH and we found 65 reported individual risk factors (supplementary table S1). For the new paediatric risk tool, we selected those variables that were reported in at least three different paediatric cohorts. In addition, four variables were included in the new risk tool, that were reported in fewer than three different cohorts, but were regarded as clinically relevant by the task force (table 4).

In summary, World Health Organization functional class (WHO-FC), tricuspid annular plane systolic excursion (TAPSE) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are most frequently shown to correlate with outcome in paediatric PAH, and all three have been validated in different and independent cohorts [8–24]. Furthermore, these were not only demonstrated to predict outcome both at diagnosis and at follow-up, but also their change in value over time proved predictive for outcome [11].

Haemodynamic variables have been studied in independent cohorts and some of these are validated prognosticators of outcome. In a recent cohort of 71 children with newly diagnosed PAH, haemodynamics obtained by cardiac catheterisation at diagnosis as well as during follow-up were evaluated [25]. At the

TABLE 3 Complex congenital heart disease associated with pulmonary vascular disease

	Examples
Anatomical (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
Multifactorial	Scimitar syndrome
Single ventricle	Unoperated with unobstructed pulmonary blood flow Fontan circulation

TABLE 4 Risk stratification tool, based on variables associated with increased risk of adverse outcomes in paediatric pulmonary arterial hypertension in at least three different cohorts of children

	Lower risk	High risk
Age[#]	Older	Younger
Clinical evidence of RV failure[#]	No	Yes
Progression of symptoms[#]	No	Yes
Growth, "failure to thrive"		
Height z-score	⩾−2	<−2
Weight z-score	⩾−2	<−2
WHO-FC	I, II	III, IV
6MWD (>6 years) m	>350	⩽350
NT-proBNP ng·L^{-1}	⩽300	>1200
Echocardiography		
TAPSE mm	⩾12	<12
RVFAC %	⩾25	<25
RVLS free wall %	⩽−17	>−17
RVLS global %	⩽−14	>−14
LVEI systole	⩽1.89	>1.89
LVEI diastole	⩽1.55	>1.55
RVd/LVd ratio[#]	⩽1	>1
RA area[#] cm^2	⩽18	>18
Pericardial effusion[#]	No	Yes
Haemodynamics		
PVRI WU·m^2	⩽11	>11
mRAP mmHg	⩽10	>10
Systemic cardiac index L·min^{-1}·m^{-2}	⩾2.5	<2.5
mPAP/mSAP ratio	⩽0.75	>0.75
PACI mL·mmHg^{-1}·m^{-2}	⩾0.9	<0.9
S_{vO_2}[#] %	⩾65	<65
Acute response Sitbon criteria	Yes	
Cardiac MRI		
RVEF %	⩾44	<44
RVMI g·m^{-2}	⩽80	>80

RV: right ventricle; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular fractional area change; RVLS: right ventricular longitudinal strain; LVEI: left ventricular eccentricity index; RVd: right ventricular diastolic dimension; LVd: left ventricular diastolic dimension ratio; RA: right atrial; PVRI: pulmonary vascular resistance index; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; mSAP: mean systemic arterial pressure; PACI: pulmonary arterial compliance index; S_{vO_2}: systemic venous oxygen saturation; MRI: magnetic resonance imaging; RVEF: right ventricular ejection fraction; RVMI: right ventricular mass index. [#]: reported in fewer than three different cohorts, but regarded as clinically relevant by expert opinion.

initial catheterisation, baseline values for PVRI, stroke volume index (SVI), pulmonary artery compliance index, and right atrial pressure predicted freedom from death, lung transplantation or Potts shunt at 5 years of follow-up. This study proposed new cut-off values for these variables to stratify for high *versus* lower risk of adverse outcome. Moreover, the study suggested that different cut-offs should be applied at follow-up than at baseline; however, this will need further validation [25].

In addition to clinical and functional variables, newer variables derived from cardiovascular imaging by either echocardiography or magnetic resonance imaging (MRI) have emerged, including ventricular functional metrics. Echocardiographic parameters include right ventricular (RV) indices, reflecting RV systolic function, such as fractional area change and longitudinal strain [21, 26–29], but also left ventricular (LV) dimensions and LV eccentricity index (LVEI), reflecting interventricular interaction. Both systolic and diastolic LVEI have been shown to predict outcome [12, 21, 29]. MRI is of particular interest, due to the ability to determine three-dimensional RV volumes and mass. Several parameters have now been shown to predict outcome in more than one cohort of children with PAH, where right ventricular ejection fraction and right ventricular muscular mass index (g·m^{-2}), are now validated in independent cohorts [30–32].

In addition to NT-pro-BNP (or BNP), both older and newer serum biomarkers have been identified in paediatric studies, but are regarded as having not yet been sufficiently validated. These include uric acid

and the insulin-like growth factor (IGF) family and related binding proteins [33–36]. IGF-binding protein 2 was associated with death, transplant or palliative shunt [36]. Markers of inflammation, a major contributor to PAH disease development, such as interleukin-6 and serum amyloid A4 are reported to predict prognosis [22, 37, 38]. The soluble suppressor of tumorigenicity (ST2) is reported to predict clinical worsening, but also to improve the predictive ability of the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk score [39]. Early changes in angiogenic biomarkers at 7 days of age have been strongly associated with the development of bronchopulmonary dysplasia (BPD) and BPD-associated PH in preterm infants at 36 weeks corrected age, but the use of such markers to predict risk for PH after premature birth requires further validation [40].

Based on these data, the paediatric risk table has been enriched with new, validated predictors of outcomes (table 4). In this new risk tool, cut-off values for the respective risk factors, identified from the literature review, are provided, although further studies are required to validate these cut-off values. Since most cut-off values discriminated for high risk of adverse outcomes rather than low risk, the two risk strata were now named high risk and lower risk (instead of low risk).

How to optimally combine multiple individual risk factors in children with PAH is currently under study. In two recent systematic reviews investigating the performance of risk scores in PAH at either one single time point or serially during follow-up, only very few reports were found that used multiparameter risk models in paediatric PAH [41, 42]. In a Dutch national cohort of children with PAH, the number of low-risk prognostic factors derived from the WSPH 2018 paediatric risk tool, identified 30% of the children as low-risk (10–13 low-risk factors), and indeed these children were shown to have a favourable outcome [43]. However, this strategy was less discriminative in the 70% of children who had <10 low-risk factors. Serial risk assessment at follow-up, using only seven noninvasive criteria, significantly improved the discriminative value (C-statistic 0.78) [43]. In a Chinese national multicentre prospective registry, a noninvasive risk tool was developed, comprising the variables weight z-score, WHO-FC and NT-proBNP (C-index 0.65 for predicting 1-year survival) [18]. Griffiths *et al.* [39] showed the prognostic abilities of the REVEAL 2.0 risk calculator in the National Heart, Lung, and Blood Institute-funded National Biological Sample and Data Repository for PAH (PAHB) and the Children's Hospital Colorado cohort. In addition, applying ST2 serum levels to the REVEAL risk calculator significantly improved the model's predictive ability (C-statistic from 0.69 to 0.78) [39]. Lammers *et al.* [12] proposed a prediction tool based on three echocardiographic variables: a combination of right atrial area z-score >2.9, left ventricular diastolic eccentricity index >1.5 and TAPSE z-score <−2.85 predicted mortality (C-statistic 0.82). However, these integrated risk tools require external validation. The European Paediatric Pulmonary Vascular Disease Network has also proposed a risk score based on previous WSPH paediatric risk tool variables [44]. Although this score correlated with cardiac MRI and advanced echo measures in an internal analysis, it was not derived from nor tested against patient outcome data.

Thus, current data suggest that in paediatric PAH, maintaining or reaching a low-risk profile during follow-up is associated with improved survival and thus justifies its clinical use as a treatment goal in paediatric PAH [43]. However, more data are necessary to assess and improve the performance of integrated risk stratification tools in children with PH. Current paediatric risk tools may be enhanced by including new prognosticators, such as imaging and serum biomarkers, and perhaps also genetic background. Furthermore, greater granularity is needed to predict the outcome of the majority of children who are not "at low-risk". Current data on prognostic markers and clinical risk scores predominantly relate to WSPH group 1 PAH in children. In children with different subgroups of PAH-CHD, or in neonates or infants with developmental lung disease and PH in other WSPH groups, very different prognosticators and risk factors may prove useful, but have yet been insufficiently studied.

Finally, recent data have shown that the genetic background in paediatric PH may affect outcomes and may be incorporated into paediatric risk stratification in the future. For example, children with a T-box transcription factor 4 (TBX4) mutation had better survival than those with a bone morphogenetic protein receptor (BMPR)2 gene mutation in one cohort [45]. Evaluation for genetic causes of developmental lung disease provides important diagnostic and prognostic information. However, this is work in progress, since the impact of individual variants is insufficiently clear on prognosis and response to treatment in childhood-onset PAH. More short- and long-term data are needed to compare outcomes with the growing list of newly described genetic abnormalities.

When compared to adult disease, paediatric-onset PH is often associated with a more severe clinical course with complex comorbidities, including heart and lung developmental anomalies [46]. Accordingly, the spectrum and contribution of genetic aetiologies differs with those of adult PH. Children have a greater

genetic burden than adults, with rare genetic factors contributing to ∼42% of paediatric-onset PAH in comparison with ∼12.5% of adult-onset PAH. *De novo* variants are frequently associated with PAH in children and contribute to ⩾15% of all paediatric cases [46]. Genetic variants may significantly affect the clinical course of pulmonary hypertension in children and perhaps impact treatment strategies. Therefore, in both neonatal and paediatric PH, genetic testing and counselling for patients and families has become more important and needs to become more actively applied in routine practice [47].

Treatment of paediatric PH

Treatment of paediatric PH continues to be hindered by the lack of randomised controlled clinical trials. In the past 5–10 years, a few clinical trials have revealed important information regarding the pharmacokinetics and safety of PAH-targeted medication in children. Most clinical trials in paediatric PAH were not designed to demonstrate clinical efficacy due to the lack of consensus on age-appropriate clinical end-points in children with PAH, in addition to limitations due to low enrolment rates in some studies (see section on regulatory considerations). Thus, the proposed treatment algorithm is based on a combination of real-world data, expert experience and extrapolation from adult clinical trials. Criteria for approval of PH medications differ between the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) (table 5). Here, we briefly describe results of recent paediatric trials leading to EMA authority approval for paediatric use.

Tadalafil, a phosphodiesterase type 5 inhibitor, was studied in a phase 3, randomised, international, multicentre, double-blind, placebo-controlled trial (followed by an open-label extension period) with an add-on to a patient's current endothelin receptor antagonist (ERA) treatment [48]. Patients received 20 or 40 mg of tadalafil or placebo once daily for 24 weeks. The primary end-point was a change in the 6-min walk distance (6MWD). However, the trial was stopped prematurely, with only 35 of the planned enrolment of 134 patients completed, so no formal statistical analysis was performed. 17 tadalafil and 18 placebo patients with a median age of 14.2 years were included in this study. In the absence of testing for statistical significance, least-square mean changes in 6MWD at week 24 were greater, with a placebo-adjusted mean difference of almost 24 m. There was a trend for a reduction in serum NT-proBNP levels with tadalafil therapy. No new adverse events were identified and there were no deaths in the trial.

The effects of add-on treatment with ambrisentan, a selective endothelin A receptor inhibitor, were studied in an open-label phase IIb study of patients aged 8–18 years and designed to demonstrate safety and efficacy [49]. Children were randomised to low (2.5 mg) or high (10 mg) doses of ambrisentan for 24 weeks. Of the planned sample size of 66 children, only 41 patients were randomised in almost 3 years. Adverse events were mild or moderate, with no apparent differences between dosing groups. Side-effects

TABLE 5 Current European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) approval status for use of pulmonary arterial hypertension drugs in paediatrics and ongoing trials

	EMA approval	FDA approval	Comments
PDE-5i			
Sildenafil	Yes	Yes	EMA: age 1–17 years FDA: age 1–17 years
Tadalafil	Yes		EMA: age >2 years
sGC stimulator			
Riociguat	Yes		EMA: >50 kg
ERA			
Bosentan	Yes	Yes	FDA: age >3 years EMA: age >1 year
Ambrisentan	Yes		EMA: age 8–18 years
Macitentan			Ongoing study
PPA			
Epoprostenol			
Treprostinil			
Selexipag (IPR-agonist)			Ongoing study
Activin signalling inhibitor			
Sotatercept			Ongoing study

PDE-5i: phosphodiesterase-5 inhibitor; sGC: soluble guanylate cyclase; ERA: endothelin receptor antagonist; PPA: prostacyclin pathway agent; IPR: selective prostacyclin receptor.

were similar to those reported in adults. There were two deaths, but both were felt to be unrelated to study treatment. Combining the two dosage groups, there was an increase in 6MWD of 41 m at 24 weeks. Functional class was maintained or improved in 70% and 27% of subjects. A long-term open-label extension study confirmed the maintenance of these results.

Soluble guanylate cyclase (sGC) stimulation with riociguat was studied in a safety and tolerability clinical trial [50]. Children aged 6–17 years in WHO-FC I–III on stable ERA or prostacyclin therapy received 0.5–2.5 mg of riociguat three times a day. 24 patients were enrolled, most of whom were WHO-FC II. Mild-to-moderate adverse event rates were similar to published adult data, and hypotension and haemoptysis were rarely recorded. Blood drug concentrations of riociguat were similar to those in adults. Only 19 out of 24 patients were able to perform a 6-min walk test, but an increase in 6MWD of 24 m and a mean decrease in NT-proBNP of 66 $pg \cdot mL^{-1}$ were reported. Overall, the WHO-FC class did not change during the short study period. However, two patients had clinical worsening of PH that required hospitalisation. Furthermore, a single-centre case series showed that young infants with neonatal PH who were unable to wean or to discontinue inhaled nitric oxide (iNO) with sildenafil tolerated the ability to lower and stop iNO with riociguat, probably due to its ability to stimulate sGC more effectively than authentic iNO itself in the setting of oxidised or dysfunctional sGC [51]. These data reveal a knowledge gap in the use of pulmonary vasodilators in neonatal PH [52–54].

Clinical trials of macitentan (a dual ERA; clinicaltrials.gov identifier NCT02932410) and selexipag (an oral non-prostanoid prostacyclin receptor agonist; clinicaltrials.gov identifier NCT04175600) are currently being performed. Several observational case series have been published regarding the use of these agents. Single-centre case series have suggested beneficial changes in BNP and echocardiographic variables with macitentan [55]. Similarly, studies of selexipag have shown improved functional class in some patients [56]. A systematic review of 14 studies of selexipag as an add-on therapy for 58 paediatric patients reported that 80% of subjects had mild-to-moderate side-effects, which were mostly related to gastrointestinal problems [57]. Although several studies reported that patients tolerated the transition from parenteral prostanoid therapy to oral selexipag and remained stable in WHO-FC I–II, observations of worsening haemodynamics and increasing NT-proBNP in these seemingly stable patients have been reported [58]. These data suggest that selexipag can have a role in the care of those patients, who do not require parenteral prostanoids or of those unable to be treated with parenteral prostanoids or frequent prostacyclin inhalations. At the same time, these data emphasise caution and not to assume selexipag as an equal substitute for parenteral prostanoids.

Recently, the first drug that interacts with the “fourth pathway” of PAH, the BMP/transforming growth factor-β pathway, was US FDA-approved for PAH in adults. Sotatercept, a ligand trap, binds activins and growth differentiation factor and restores the balance between pro-proliferative and anti-proliferative BMP pathways [59–61]. Clinical trials in children are ongoing (clinicaltrials.gov identifier NCT05587712).

Due to many challenges in developing and completing multicentre randomised controlled trials in children with PH and the lack of robust scientific evidence on efficacy and safety, not all PAH medications have been approved for paediatric use by the regulatory authorities (table 5). Nevertheless, they are widely used in diverse forms of paediatric PH, and are included in the proposed treatment algorithm for paediatric PAH. In contrast to PAH in adults, data are limited in paediatric PAH on the effects of different combination therapy regimens (sequential *versus* upfront combination). A current multicentre randomised controlled trial from the Pediatric Pulmonary Hypertension Network is underway, which randomises WSPH group 1 and group 3 PH children to mono *versus* duo therapy at the time of PH diagnosis (clinicaltrials.gov identifier NCT04039464) [62]. Thus, the current pharmacological approach of paediatric PH remains challenging and is based mainly on real-world data and expert consensus statements on the off-label use of PAH treatments combined with the extrapolation of data from large adult randomised controlled studies. Based on these considerations, recent PAH European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend adopting comparable therapeutic algorithms in children and adults [63].

We propose a pragmatic treatment algorithm based on the following assumptions.

1) The relevance of maintaining a risk-oriented treatment approach using the lower risk of mortality as a therapeutic target.
2) The superiority of combination therapy *versus* monotherapy in idiopathic PAH (IPAH), hereditary PAH (HPAH) and drug- or toxin-induced PAH (DT-PAH) (supported by retrospective, observational paediatric cohort studies) [10, 43, 64–66].

3) The algorithm is most applicable in children with IPAH and HPAH; however, in children, the clinical picture is usually more complex and heterogeneous due to the diversity of diseases associated with PH. Comorbidities are frequent, including CHD, developmental lung diseases, especially BPD, congenital diaphragmatic hernia (CDH) and others, including rare chromosome, genetic and syndromic disorders (such as Down syndrome, surfactant protein gene abnormalities, alveolar capillary dysplasia, TBX4 mutations and others). Different potential pathophysiological components of PH may coexist in these patients, overlapping different PH clinical groups.

Ideally, PH therapy in infants would have a tailored treatment plan for the different disease processes that contribute to PH. Due to the rarity and complexity of PH in children, expert referral for interdisciplinary care is particularly relevant. An accurate and exhaustive diagnostic workup to identify the potential mechanisms leading to PH and its progression is required, and confirmatory heart catheterisation should be included.

General measures (including physical activity and immunisation) and background treatments (including oxygen, digoxin and diuretics) should be considered on an individual basis and tailored throughout the course of the disease. Anticoagulant therapy (vitamin K-antagonists, direct oral anticoagulants) or antiplatelet therapies are generally not indicated for PH in subjects without specific concerns for thromboembolic complications.

The further targeted treatment strategy is identified according to the clinical picture (figure 1). To emphasise that paediatric patients with cardiopulmonary comorbidities require a different approach from that adopted in patients with isolated PAH, the algorithm includes a specific section for these infants and children.

Among patients without cardiopulmonary-associated conditions, acute vasoreactivity testing (AVT) is recommended in IPAH, HPAH and DT-PAH, to detect those who may benefit from calcium channel blocker (CCB) therapy [67]. For IPAH/HPAH/DT-PAH responders to AVT by the Sitbon criteria, the initial therapeutic management comprises high-dose CCB therapy (figure 1a), which requires close follow-up, as some patients may fail long-term therapy; those who reach and maintain near-normalisation of haemodynamics on CCB therapy probably have the best prognosis. In case of inadequate response, defined by the disappearance of vasoreactivity, worsening haemodynamics and/or features of a “high risk profile”, PAH targeted therapy should be added on top of CCB therapy. It is recommended that CCB therapy is not stopped in these patients [68].

A therapeutic strategy based on risk stratification and treatment response is proposed in patients with isolated PAH without cardiopulmonary-associated conditions (figure 1b). In patients who present at high risk of death, initial parenteral therapy with intravenous/subcutaneous prostacyclin analogues is recommended and rapid combination with a phosphodiesterase-5 inhibitor (PDE-5i) and/or an ERA has to be considered. In addition, early consultation for lung transplantation and interventional palliative procedures must be suggested [69]. For patients presenting at lower risk, initial therapy consists of the upfront or sequential combination of oral agents (ERA+PDE5-i).

Regular monitoring of treatment effects and disease progression is crucial. Achieving and maintaining a low-risk profile should be considered an adequate treatment response. In the event of an inadequate treatment response, escalation to maximal combination therapy is recommended with early consideration of lung transplantation and interventional palliative procedures in patients receiving triple combination therapy including parenteral (*i.v*/*s.c.*) prostacyclin analogues and/or in the presence of high-risk features.

The new treatment algorithm includes an arm, dedicated to PAH and cardiopulmonary comorbidities, including developmental lung disorders and congenital systemic–pulmonary shunt which currently represent the most frequent conditions associated with PH in children.

The use of therapies for PAH is common in infants with developmental lung disease (group 3 PH), but currently not US FDA or EMA approved, as the effects of PAH therapies on outcomes in this population are unclear, and data enabling robust treatment recommendations are lacking. Developmental lung diseases include a variety of disorders that are currently classified within group 3 PH (table 6). BPD and CDH are the most common conditions included in this group. The prevalence of PH increases in step with the severity of developmental lung disease, and it may disappear in time with lung growth, although persistence and worsening of PH have been reported in older children and young adults even in the absence of significant clinical lung disease [70–72]. Potential favourable effects of PAH therapies are

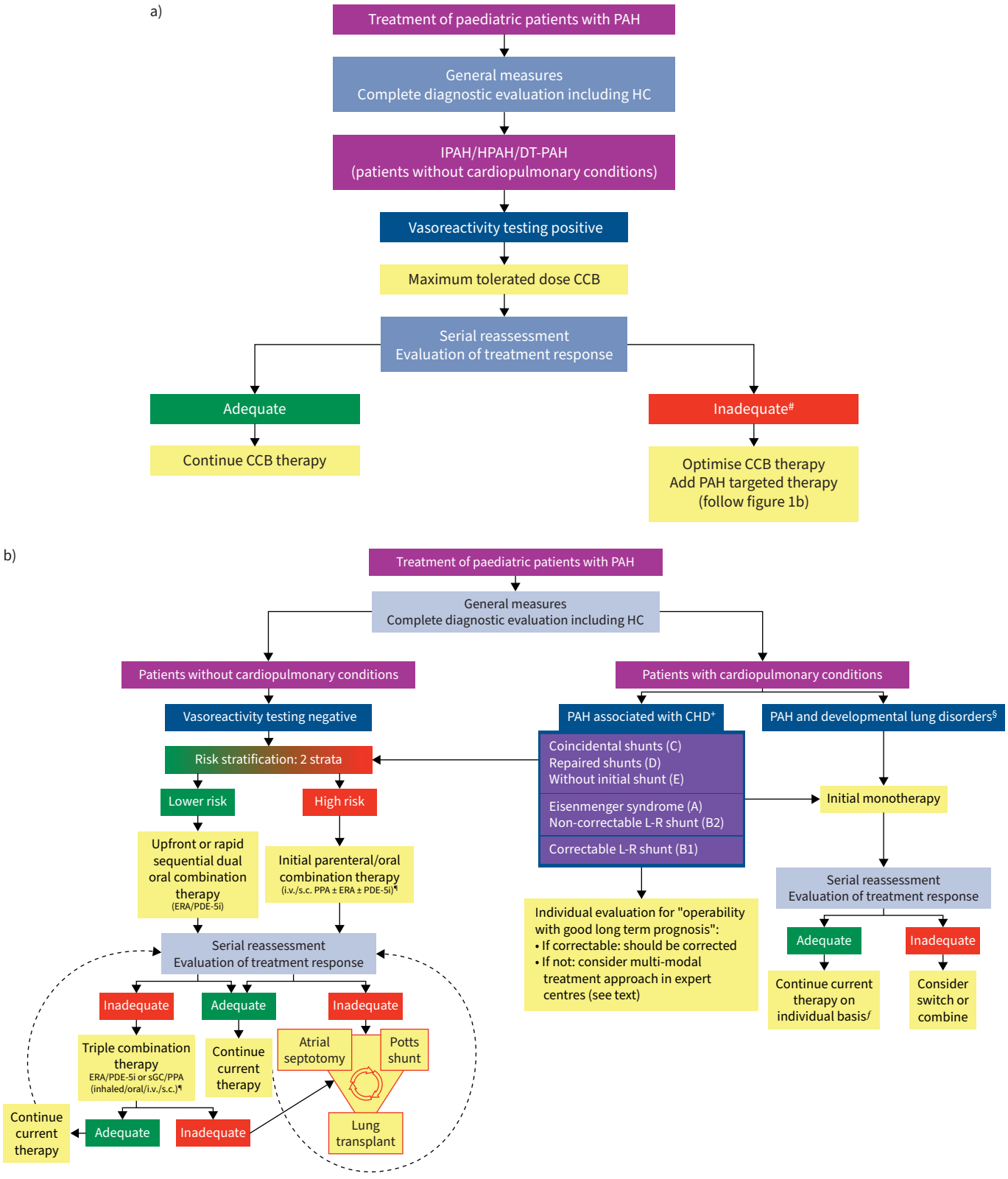


FIGURE 1 Treatment strategy for paediatric patients in pulmonary arterial hypertension (PAH). a) Treatment for children with idiopathic PAH (IPAH)/hereditary PAH (HPAH)/drug- and toxin-induced PAH (DT-PAH) and positive acute vasoreactivity testing. b) Treatment for children with IPAH/HPAH/DT-PAH and negative acute vasoreactivity testing and for children with PAH and associated cardiopulmonary conditions. HC: heart catheterisation; CCB: calcium channel blocker; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitor; PPA: prostacyclin pathway agent; sGC: soluble guanylate cyclase; CHD: congenital heart disease; L: left; R: right. #: inadequate long-term response to CCB (see text);

[¶]: suggest early consultation for lung transplant/Potts shunt; [+]: according to clinical classification of PAH associated with CHD: group A, Eisenmenger syndrome (A); group B, PAH associated with prevalent systemic-to-pulmonary shunts: correctable (B1); noncorrectable (B2); group C, PAH with small/coincidental defects (C); group D, PAH after defect correction (D); group E, PAH associated with CHD without (prolonged) initial shunt; [§]: developmental lung disorders: the underlying lung disease should be aggressively treated and respiratory support optimised before considering PAH therapy (includes bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia, neonatal chronic lung disease); [ƒ]: patients with developmental lung disorders, especially BPD, may normalise pulmonary pressure over time and might be weaned from PAH-targeted therapy with close monitoring.

expected in patients with severe pre-capillary PH and mild lung disease, in whom the increase of PVRI is mostly associated with the presence of intrinsic pulmonary vascular disease.

An appropriate selection of patients eligible for PAH therapy is mandatory. In this arm of the treatment algorithm, patients with confirmed pre-capillary PH and respiratory impairment should be included. In the absence of cardiac catheterisation in the neonate, caution is urged to make the diagnosis pre-capillary PH as diagnosed by echocardiography alone and the potential role of other physiological mechanisms involving post-capillary disease, such as LV diastolic dysfunction or pulmonary vein stenosis, should be ruled out. The underlying lung disease should be primarily treated (such as hypoxia, aspiration, central airways disease and airways hyperreactivity), and respiratory support should be optimised when considering PAH therapy [73]. Initial monotherapy, regular serial reassessment and further individualised switch or combination therapy are proposed for most patients with pre-capillary PH and developmental lung disease. Especially in children with BPD-associated PH, PH may resolve over time, and medication might be cautiously withdrawn [74–76].

PAH associated with CHD represents a heterogeneous patient population: it includes five clinical groups, each requiring a specific therapeutic approach (table 2). PAH patients with small coincidental defects (group C), with repaired CHD (group D) and without initial shunt (group E) are managed as group 1 PAH. For patients with Eisenmenger syndrome and noncorrectable left-to-right shunts (groups A and B), initial monotherapy, regular serial reassessment and further individualised combination therapy are proposed; patients with correctable left-to-right shunts require individual evaluation for defect correction (figure 1b).

Strategies for managing advanced disease in children: roles for reverse Potts, septostomy or transplant

Children with severe PAH who have failed conventional targeted PH medical therapy have limited therapeutic options. The appropriate course to take depends on many factors. Resources, access and experience of the advanced PH centre are key. In some centres, continuous prostacyclin and transplantation

TABLE 6 Developmental lung diseases associated with pulmonary hypertension

Bronchopulmonary dysplasia
Congenital diaphragmatic hernia
Down syndrome
TBX4 genetic disease
Alveolar capillary dysplasia with “misalignment of veins” (FOXF1 gene)
Lung hypoplasia (omphalocoele, prolonged rupture of membranes, renal agenesis, idiopathic, other clinical settings)
Congenital acinar dysplasia
Surfactant protein abnormalities
Surfactant protein B deficiency
Surfactant protein C deficiency
ABCA3
TTF-1/Nkx2
FLNA
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

TBX4: T-box transcription factor 4; FOXF1: forkhead box protein F1 variants; ABCA: ATP-binding cassette A; TTF: thyroid transcription factor; Nkx: NK2 homeobox; FLNA: filamin A.

are not an option. In these cases, atrial septostomy has been shown to prolong survival and can be done safely within the limits of the severity of right heart failure [77, 78]. In other centres, lung or heart–lung transplantation has become the primary option due to long-term experience with patients with severe PH. A newer option for the child failing medical therapy includes a "reverse" Potts pulmonary artery to systemic shunt. Typically, a connection is made between the pulmonary artery and the descending aorta as a systolic "pop-off" for the pulmonary circulation.

In some countries, atrial septostomy has been a mainstay of therapy for the child or adult failing available conventional medical therapy [77, 78]. Advances in technique have allowed this to be done safely and have shown prolonged survival. Atrial septostomy may also play a role in a child with subsystemic PAP who has recurrent syncope [79, 80]. In this case, a temporary pop-off allows for right-to-left shunting to prevent syncope. Interestingly, in the catheterisation laboratory, many of these patients with syncope are vasoreactive to pulmonary vasodilators, such as iNO and the shunt may provide relief during abrupt vasoreactive rise in PAP [79]. As the Potts shunt has become more prevalent, the use of atrial septostomy in patients with suprasystemic PAH has decreased. This scenario might be modified with a lower threshold to perform a reversed Potts shunt in countries where other advanced therapies are unavailable. The Potts shunt may also be used in children being considered for lung transplantation as a palliative bridge or as destination therapy when a transplant is unavailable or contraindicated. Although the use of an atrial septostomy before the Potts shunt is not contraindicated, the additional right-to-left shunting at the atrial level may cause worsening systemic saturation with a right-to-shunt at an atrial level in addition to the right-to-left shunt at the Potts shunt [81]. The decision about whether to close an atrial shunt at the time of surgery should be discussed *a priori* and adapted as needed during surgery if the patient still requires a small atrial level shunt.

The Potts shunt was reimagined in the early 2000s initially in a patient with transposition of the great arteries who developed severe PAH after an arterial switch [82]. The concept was that a systolic shunt might allow for decompression of the suprasystemic RV, as well as preservation of coronary artery and brain oxygenation. This procedure has undergone several different iterations. Initially, the procedure was performed *via* a lateral thoracotomy with a direct connection between the left pulmonary artery and the descending aorta [82], as initially described by Willis Potts. As the procedure was increasingly utilised, the concept of a valved conduit between the pulmonary artery and aorta became increasingly accepted [83]. Four-dimensional flow cardiac MRI revealed there could be a significant left-to-right shunt, usually in diastole, in some patients [84, 85]. Therefore, a valved conduit was proposed and is used increasingly. Further, the valved shunt is more easily placed from the front sternal approach in older children. This may also decrease the development of collaterals and adhesions in the chest, which may be problematic if later lung transplantation is needed [86, 87]. There are some centres who will not perform a lung transplant after a Potts shunt, so all options should be considered when deciding to pursue a reversed Potts shunt.

The international Potts registry of 110 patients brought forth important information about the success and limits of the Potts pulmonary-to-systemic arterial shunt [87]. The overall 1- and 5-year freedom from death or transplant rates were 77% and 58%, respectively, and 92% and 68%, respectively, for those discharged home. Very high mortality was noted in patients who were on extracorporeal membrane oxygenation (ECMO) at the time of the shunt surgery, were admitted to the intensive care unit (ICU) and were on mechanical ventilation. Percutaneous shunt has been proposed in patients with tiny restrictive arterial ducts that can be enlarged with stents [88]. Percutaneous Potts shunt by direct puncture of the aortic and pulmonary walls has also been performed [89]. While the first technique is technically simple, the second carries a high risk. For these two techniques, repeated procedures are necessary to progressively dilate the stent during the child's growth.

Despite growing experience worldwide, several questions remain with regard to the indications for a Potts shunt, as follows.

1) Right ventricular function: are there indicators that a Potts shunt or the RV may fail if the RV function is too low at the time of surgery since the RV will need to be able to generate systemic level pressures for the shunt to work effectively?
2) Atrial shunt closure: should atrial defects be partially or fully closed at the time of the Potts shunt?
3) Indications and access: at the time of presentation, what are the indications for lung transplantation rather than a Potts shunt?
4) Timing of transplant evaluation: due to the complexity of these procedures and the potential for the need for lung transplantation, should a lung transplant evaluation be performed at the same time as consideration of a Potts shunt? This is important, as transportation of the patient with a failed shunt on ECMO is challenging.

Lung transplantation has been a mainstay of treatment for severe PH for many decades. Advances in lung transplantation, technique and management have improved lung transplantation outcomes, but they are still suboptimal long-term. As stated before, the decision to perform a lung transplant instead of a Potts shunt may be difficult and depends on many factors, including age, RV function, patient location, resources and insurance approval. Recent data have described improvement in lung transplantation and Potts survival, with waitlist mortality decreasing from 52.6% to 13.6% and 5-year survival increasing from 57.1% to 74.7% after Potts and from 55.6% to 77.2% after transplantation [86]. However, experts agree that early referral for lung/heart–lung transplant evaluation in children who have access to transplantation and who remain high-risk despite optimisation of medical therapy is indicated [69].

There are no universal guidelines for selection of which patient who has failed conventional medical therapy should undergo atrial septostomy, lung transplantation, a Potts shunt or a sequential combination of these approaches. A multidisciplinary team should generally evaluate the patient and determine the best course. These evaluations should include an assessment of risk factors, technical considerations, available expertise and the possible sequence of interventions (figure 1b).

Risks of atrial septostomy increase in cases of severely elevated right atrial pressure, baseline cyanosis or associated severe parenchymal lung disease, and increased thromboembolic risk. The risk of Potts shunt increases in cases of RV failure, ECMO, ICU admission and mechanical ventilation. Furthermore, awareness of the policies at the local transplant centre is needed, for the feasibility of performing lung transplantation after Potts surgery. A decision to go straight to transplantation evaluation should occur if the patient is not a candidate for either a Potts shunt or septostomy despite optimal medical therapy. Future studies of patients failing conventional medical therapy will be important to better define the indications and contraindications for each procedure.

"Treat and repair" is too simple: time for multimodal treatment to optimise long-term outcome in paediatric borderline PVR-CHD

"Treat and repair" is a term that has been used and has been generally aimed at ultimate repair of the congenital heart defect in patients with "borderline" pulmonary vascular resistances (PVRI 4–8 WU·m^2). However, this approach does not account for the heterogeneity and complexity of the physiological features that can characterise the patient with borderline PVR-CHD. Furthermore, some patients start out with borderline PVR-CHD and others achieve this benchmark with targeted medical therapy. This oversimplified "treat and repair" approach requires further understanding and clarification and perhaps a new nomenclature of "borderline PVR-CHD" as a subset of inoperable patients with CHD.

In the current era, with surgical and medical advances, we may be able to more readily manage a borderline PVR-CHD patient through surgical repair. However, short-term survival after closure of a cardiac shunt is not sufficient and should not be the ultimate goal of treatment. One needs to recognise that these patients can decompensate with RV failure and have poor long-term outcomes if their pop-off shunt has been completely eliminated, converting these subjects into a PAH-CHD, group D phenotype (table 2). In contrast, an approach that includes partial repair may be more appropriate in a borderline PVR-CHD case.

This task force emphasised the importance of goal-directed multimodal (medical/interventional/surgical) approach to these patients, which aims for improved haemodynamics post-operatively/post-intervention and leads to slowing down or stopping progression of the pulmonary vascular disease for the long-term in addition to improving overall quality of life. The patient should be optimised medically before consideration of this approach. Once optimised and in the "borderline range", how then do we determine which patients with borderline PVR-CHD might be eligible for partial repair of their CHD? First, there is not one simple metric, such as for instance PVR, that can predict success. In general, baseline haemodynamics help predict success for the closure of simple congenital cardiac defects together with other parameters such as younger age and location of the shunt [90]. However, there are several other factors that may indicate a more favourable clinical phenotype for considering partial repair of CHD in a borderline PVR-CHD patient (table 7). Patients with Eisenmenger physiology (group A) should not be considered for this approach. Previous recommendations have suggested that patients with a baseline PVR <5–6 WU and pulmonary-to-systemic vascular resistance ratio (R_p/R_s ratio) <0.3, as well as pulmonary-to-systemic blood flow ratio (Q_p/Q_s ratio) >1.5 and normal saturations, were candidates for surgery [63, 91–93]. Children with PVRI >8 WU·m^2 are probably inoperable, while those PVRI <4 WU·m^2 could undergo shunt closure. The grey zone for operability or "borderline" haemodynamics is in the 4–8 WU·m^2 range within which individualised decision-making is suggested [92]. The proposed threshold for operability of adult patients with left-to-right shunts is baseline PVR <3 WU. The current ESC/ERS guidelines add that for an adult patient with an ASD and baseline PVR >5 WU, a fall below 5 WU after PAH-targeted therapy allows closure of the shunt

TABLE 7 Pulmonary arterial hypertension associated with congenital heart disease (CHD) and the operability grey zone: "borderline" pulmonary vascular resistance (PVR)-CHD (with elevated PVR)

Good surgical candidate (suggested thresholds)	PVRI <4 WU·m^2 or baseline PVR <5–6 WU
	R_p/R_s ratio <0.3
	Q_p/Q_s >1.5 and
	Normal oxygen saturations at rest and with exertion
"Borderline" PVR-CHD (the grey zone)	PVRI 4–8 WU·m^2 range
Inoperable	Children with PVRI >8 WU·m^2 are probably inoperable
	Decreased oxygen saturations at rest or with exertion

PVRI: indexed pulmonary vascular resistance; WU: Woods Units; R_p/R_s ratio: pulmonary-to-systemic vascular resistance ratio; Q_p/Q_s: pulmonary-to-systemic blood flow ratio

[63, 94–101]. The limited data on haemodynamic predictors of long-term outcomes adjusted for patient's characteristics as well as shunt physiology clearly indicate that there is not one single criterion to indicate closure of shunts with elevated PVR. This question is of particular importance as inappropriately closing a shunt can impair long-term outcomes as illustrated by the poor outcome of patients with PAH-CHD of group D (after shunt closure).

Additional information beyond baseline haemodynamics has been explored to further define operability or prognostic. Acute vasodilator testing, which lowers PVRI and raises Q_p/Q_s to these mentioned levels, may also aid in determining operability; however, they should not be used in isolation if other features are unfavourable. Several series have shown that a simple evaluation demonstrating a fall in oxygen saturation during exercise is a poor prognostic factor for complete repair [102]. Novel markers such as higher levels of circulating endothelial cells or progenitor cells [103, 104] or the switch from a proliferative vascular phenotype to one of senescence [105], have been associated with outcomes and may be used in the future. Consequently, a multidisciplinary and multiparameter approach to individualised patient decision-making is recommended regardless of patient age and requires close long-term follow up. After deep phenotyping of an individual patient, the strategy may use multiple tools in various sequences: PAH-targeted therapy, surgical or percutaneous complete or partial closure of cardiac shunts, pulmonary artery banding and others (table 8).

TABLE 8 Intervention in paediatric "borderline" pulmonary vascular resistance associated with congenital heart disease

Favourable parameters for consideration of intervention	
Clinical	Absence of cyanosis (at rest and with exertion)
	Younger age
Anatomical	Pre-tricuspid shunt (*e.g.* ASD)
	Multilevel shunts
Haemodynamic	PVRI <4–8 WU·m^2 with reduction on targeted PH therapy and rise in Q_p/Q_s to ⩾2:1
Echocardiographic	Absence of right-to-left shunt
Absence of signs of RV failure	
Toolbox of interventional/surgical approaches	Targeted PAH medical therapies
	Pulmonary arterial banding
	Percutaneous closure of a congenital systemic–pulmonary shunt (*e.g.* ductal occluder)
	Percutaneous downsizing of an ASD (AFR, fenestrated ASD device)
	For multilevel shunts: closure of one defect only leaving a residual shunt
	Surgical repair of a congenital systemic-pulmonary shunt with intentional residual fenestration

RV: right ventricular; ASD: atrial septal defect; PVRI: indexed pulmonary vascular resistance; WU: Wood Units; PH: pulmonary hypertension; Q_p/Q_s: pulmonary-to-systemic blood flow ratio; PAH: pulmonary arterial hypertension; AFR: atrial flow restrictor.

In a select group of 30 paediatric patients with CHD and a PVRI ⩾3 WU·m^2 [94] including ASD (30%), ventricular septal defect (VSD) (7%), patent ductus arteriosus (19%) or multiple shunts (47%), mPAP, PVRI and R_p/R_s decreased after PAH-targeted therapy, including a median drop in PVRI from 7.1 WU·m^2 at diagnosis to 3.8 WU·m^2. Of note, the institutional policy for fenestration at the time of shunt closure in the paediatric cohort included 1) those requiring dual or triple therapy; 2) *i.v.* prostanoid pre-operatively; 3) RV dysfunction; and 4) PVRI >5 WU·m^2 at the time of diagnosis. 80% of patients underwent fenestration, and only one patient died, with a follow-up of an average of 6 years. A "repair and then medically treat" strategy has also been described, but was not demonstrated to be more favourable than medically treating prior to an interventional/surgical procedure [106].

Clearly, there is no single universal approach to patients with borderline PVR-CHD. Current understanding of the optimal approach to these patients is further limited, as long-term data with follow-up of more than 5–10 years from repair are lacking. Furthermore, the data on post-tricuspid shunts and complex lesions are limited. The term "treat and repair" does not embrace the whole clinical picture. We propose using the broader concept of multiparameter/individualised assessments (oxygen saturation at exertion, baseline haemodynamics, acute vasodilatation testing, biomarkers, history of shunt, imaging, *etc*.) and multimodal personalised treatment for borderline PVR-CHD (PAH-targeted therapy, surgery, percutaneous interventions, fenestrations, banding, *etc*.). In addition, we suggest that serial reassessment is required, to analyse the effects of each intervention and to redirect strategy as needed.

Regulatory considerations in PH drug therapy in children

Designing and completing successful clinical trials in paediatric PH faces multiple hurdles. The most relevant are the rarity of the disease, its progressive and often dismal outcome, the lack of age-appropriate end-points, and lack of equipoise due to the off-label use of already approved adult therapies or drugs mentioned in the current guidelines, and competition between ongoing trials. The European Medical Association supports the extrapolation from adult studies because of the shared common features between children and adults. However, the ability to translate results from adult data to even younger infants and children is especially challenging. The European Medical Association is working on a new proposal to design paediatric PAH studies. The US FDA still requires a formal randomised controlled trial (RCT) with a significant clinical end-point.

For these reasons, various potential approaches have been suggested to overcome these problems and respond to the authorities' requirements for approval. These approaches include 1) a single pivotal-outcome RCT; 2) a large pharmacokinetic study with secondary clinical end-points and population pharmacokinetic modelling to extrapolate exposure from adults to paediatric patients with a pharmacodynamic similarity assessment; 3) exercise studies with mainly 6-min walk test as end-point; and 4) pharmacokinetic data complemented by exploratory efficacy data.

The lack of suitable end-points for a feasible trial remains a major challenge in designing RCTs in paediatric PAH. Recently, the US FDA discussed the possibility of using bridging biomarkers for new drug approval in children, stating that "in the case where an intervention reliably has been established to be safe and effective in adults and where there is substantive evidence that disease processes in paediatric and adult settings are biologically similar, a 'bridging biomarker' should satisfy three additional criteria: effects on the bridging biomarker should capture effects on the principal causal pathway through which the disease process meaningfully influences 'feels, functions, survives' measures; secondly, the experimental intervention should not have important unintended effects on 'feels, functions, survives' measures not captured by the bridging biomarker; and thirdly, in statistical analyses in adults, the intervention's net effect on 'feels, functions, survives' measures should be consistent with what would be predicted by its level of effect on the bridging biomarker" [107]. However, to date, there is no established "bridging biomarker" for use for application in paediatric PH.

Using invasive haemodynamics as an end-point may be a good approach, allowing results with an acceptable number of patients. However, using haemodynamics as an end-point for this disease faces the problem of not being accepted because of the potential risks of the procedure if performed only for the study. Currently, there are no clinical guidelines on the frequency of follow-up catheterisation in paediatric PH.

Based on current knowledge and practice, none of these possibilities is easy to develop. Recent event-driven RCTs using strong end-points such as time to clinical worsening have faced major recruitment problems and fewer than expected events, leading to prolonged studies, potentially without definitive results, that are not well accepted by participants and agencies.

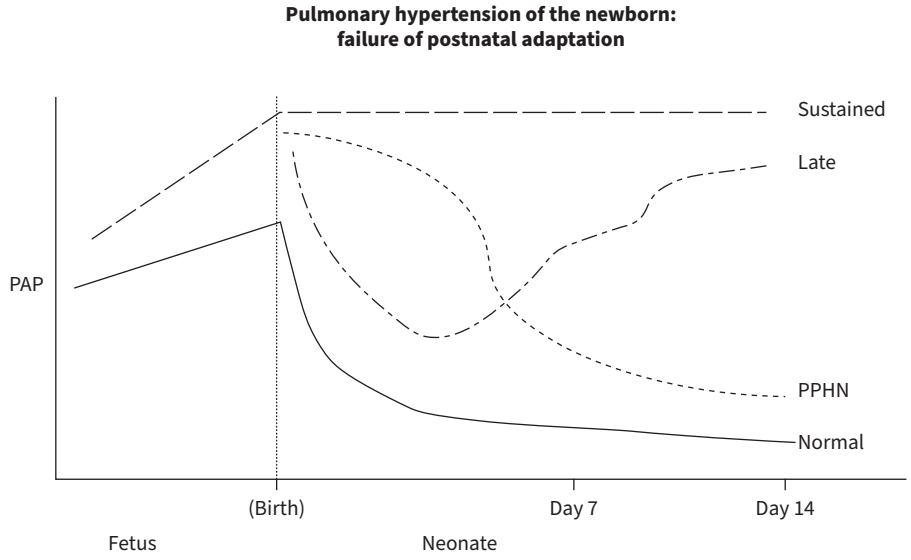
We still do not have the perfect trial design for paediatric PAH. We must develop new ideas to enrich strategies and novel surrogates to obtain data and develop treatment strategies. Accelerometery may provide age-appropriate measures of functional status, but this measure has not been validated as an end-point, and an expected treatment effect is unknown [108–110]. Extrapolation from adult studies using paediatric data is promising. This work should involve physicians, caregivers, authorities, industry, patients, parents and patient associations.

Neonatal PH

Since the 6th WSPH in 2018, numerous advances with extensive clinical studies have advanced our understanding of the diagnosis and management of diverse forms of neonatal PH, especially concerning 1) developing a more specific and pragmatic definition of neonatal PH and its phenotypes in various clinical settings during the first weeks of life; 2) the growing recognition of the importance of serial neonatal echocardiography by the neonatal community; 3) diverse physiological phenotypes and late cardiorespiratory disease associated with PH in preterm infants; and 4) genetic-based developmental lung diseases.

The normal neonatal lung circulation undergoes striking declines in PVR and PAP immediately at birth, which is essential for allowing the marked rise in pulmonary blood flow for normal cardiorespiratory transition from fetal life. In some infants, PVR and PAP remain elevated, leading to striking hypoxaemia due to extrapulmonary right-to-left shunting of blood across the patent ductus arteriosus (PDA) and/or foramen ovale, which is known as persistent pulmonary hypertension of the newborn (PPHN) [111] (figure 2). Although listed in the WSPH classification as group 1 PAH, PPHN is a physiological syndrome and includes disorders, such as developmental lung diseases, which are included in group 3. Whereas PPHN has historically been largely considered in term or near-term infants, recent studies have highlighted even higher rates of PH in preterm infants during the early postnatal period [74]. As cardiac catheterisation can have additional risk in the neonate, echocardiography is frequently used to diagnose PH.

Echocardiographic diagnosis of PH in the neonate is not one single metric, but requires an integrative approach of various supportive echocardiographic features that should be interpreted within the context of pathophysiological considerations (table 9). Although echocardiographic measures suggest an elevation of PAP, current parameters do not sufficiently define the underlying pathophysiology of increased PAP (figure 2). For example, a patient with a large ventricular septal defect may have an elevation of mPAP, but a significant increase in left-to-right flow without elevated PVR. Other causes of elevated PAP pressure may include left atrial hypertension due to left ventricular diastolic dysfunction (LVDD), pulmonary vein stenosis or mitral stenosis (PH group 2 characteristics), severe parenchymal lung disease



Early/transient (group 1 PH)
- Idiopathic PPHN
- Prematurity
- Meconium aspiration
- RDS
- Pneumonia
- Congenital heart disease
- Left ventricular dysfunction
- Vein of Galen AVM

Late/sustained (group 3 PH)
- Developmental lung diseases:
  - Prematurity/BPD
  - CDH
  - Down syndrome
  - Lung hypoplasia
  - ACD-MPV
  - TBX4
  - TTF-1/NKX2
  - Surfactant protein genetic disorders

FIGURE 2 Failure of postnatal adaptation in pulmonary hypertension of the newborn. PAP: pulmonary arterial pressure; PPHN: persistent pulmonary hypertension of the newborn; RDS: respiratory distress syndrome; AVM: arteriovenous malformation; BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; ACD: alveolar capillary dysplasia; MPV: misalignment of pulmonary veins; TBX4: T-box transcription factor 4 variants; TTF: thyroid transcription factor; NKX: NK2 homeobox.

TABLE 9 Echocardiographic assessment of pulmonary hypertension in the neonate

Echocardiographic indicators of pulmonary hypertension	Evidence of extrapulmonary right-to-left shunting at a PDA, across the atrial or ventricular level Continuous left-to-right shunting through a PDA with a maximum velocity <2.0 $m \cdot s^{-1}$ Tricuspid regurgitation velocity >2.8 $m \cdot s^{-1}$ and/or estimated sPAP more than half of the systemic arterial pressure Early diastolic pulmonary regurgitation velocity >2.3 $m \cdot s^{-1}$ Flattening of the ventricular septum and increased LVEI Shortening of the pulmonary artery acceleration time Right ventricular hypertrophy (inappropriate for age) Right atrial enlargement
Physiological targets	Exclude congenital heart disease and potential ductal-dependent lesions Appraise pulmonary haemodynamics (differentiate between contributions of high flow, pulmonary vascular resistance and/or pulmonary venous congestion) Define predominant PDA flow direction Assess pulmonary vein systolic/diastolic velocities and Doppler Assess right ventricular systolic and diastolic function (measure RVFAC, TAPSE, RVO; DTI s', e', a') Assess LV systolic and diastolic function (determine LVEF, E/A ratio, IVRT; DTI s', e', a') Determine PAATi or RVET/PAAT ratio

PDA: patent ductus arteriosus; sPAP systolic pulmonary arterial pressure; LVEI: left ventricular eccentricity index; RVFAC: right ventricular fractional area change; TAPSE: tricuspid annular plane systolic excursion; RVO: right ventricular output; DTI: Doppler tissue imaging; IVRT: isovolumic relaxation time; LVEF: left ventricular ejection fraction; PAATi: pulmonary artery acceleration time indexed to heart rate; RVET: right ventricular ejection time.

with either marked hyperinflation or atelectasis (PH group 3) or increased left-to-right flow across the PDA, ASD or VSD, or a combination of these factors. Thus, an elevation of PAP by echocardiography does not sufficiently define the presence of pulmonary vascular disease or elevated PVR. An abnormal echocardiogram in the neonate and serial changes with evolving cardiorespiratory disease must be considered in the context of other physiological factors that may increase PAP, as described, and clinical decision-making for neonatal PH requires careful assessments of heart, lung and other vascular factors, which may include the need for cardiac catheterisation for more precise care (figure 3).

As noted in a previous WSPH report [1] and other consensus statements [2, 91, 92], the standard definition of PH is generally applied to young infants after 3 months of age, as the early neonatal period is a highly dynamic period with both variable changes in PAP during the first weeks of postnatal life. However, by 3 months of age, pulmonary haemodynamics are usually like those established at other postnatal ages. Although changes in oxygenation can be associated with PH, assessments of oxygenation alone are not specific for PH-related physiology during the transition and do not sufficiently differentiate between PPHN or PH from lung disease *per se*. Thus, there remains a need for developing more precise physiological characterisation of changes in PAP and PVR during the early weeks after birth, as well as a better understanding of the clinical value of identifying different patterns of changes in PAP in term and preterm infants and related physiological implications. Standardising definitions of PH during the first weeks of life will provide useful markers to guide clinical care. It may further enhance clinical research, especially in preterm infants with concerns for mixed roles for pulmonary vascular disease, high intrapulmonary blood flow from shunts, left ventricular dysfunction and evolving lung disease to follow [112, 113].

A physiology-driven approach to neonates with PH is mandatory to improve outcomes [113]. Comprehensive, repeated evaluations of cardiac function, ductal flow and pulmonary haemodynamics are needed to achieve individualised, physiology-driven approaches to cardiovascular management in sick newborns (table 9) [112, 114–117]. A team approach including the neonatologist, pulmonologist and cardiologist is best, not only for enabling a diagnosis of PH and defining critical haemodynamic issues, but also to provide ongoing interdisciplinary care throughout the patient's neonatal ICU course and with longitudinal follow-up. Due to the rapid changes in the cardiorespiratory course, especially during the early postnatal period, serial echocardiographic evaluations provide the ability to assess the best needs and responses to therapeutic interventions (table 9). Recent guidelines for establishing successful programmes

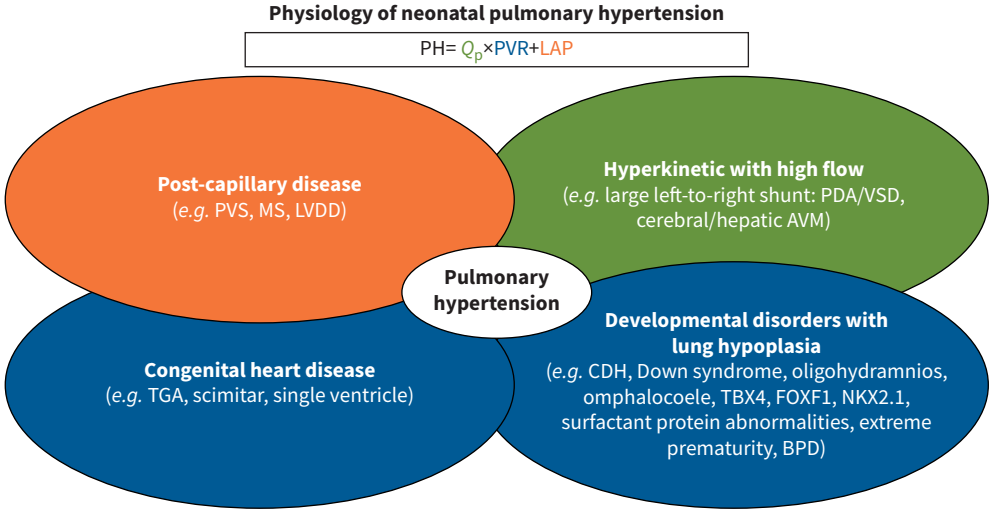


FIGURE 3 Physiology of neonatal pulmonary hypertension (PH) (increased pulmonary arterial pressure). Q_p: pulmonary blood flow; PVR pulmonary vascular resistance; LAP: left atrial pressure; PVS: pulmonary vein stenosis; MS: mitral stenosis; LVDD: left ventricular diastolic dysfunction; PDA: patent ductus arteriosus; VSD: ventricular septal defect; AVM: arteriovenous malformation; TGA: transposition of the great arteries; CDH congenital diaphragmatic hernia; TBX4: T-box transcription factor 4 variants; FOXF1: forkhead box protein F1 variants; NKX2.1: NK2 homeobox 1 variants; BPD: bronchopulmonary dysplasia.

have been published and highlight the need for extensive interdisciplinary training in echocardiography and working closely with experienced paediatric cardiologists and their team [114, 116].

One of the best examples of the potential impact of well-established protocols by sequential targeted neonatal echocardiography programmes was reported recently as applied to preterm infants [114]. This study showed that serial echocardiograms that integrate echocardiogram-based assessments of pulmonary haemodynamics, PDA status and systemic cardiovascular function with targeted interventions were associated with a 40% reduction in death or severe intraventricular haemorrhage as well decreased comorbidities, such as BPD and necrotising enterocolitis [114]. Overall, these exciting findings support the need for greater precision in defining physiological phenotypes to better target selective strategies that can reduce mortality or modulate the development of such critical morbidities as intraventricular haemorrhage, necrotising enterocolitis and BPD. The success of this haemodynamic model is linked with the performance of high-quality, well-standardised and extensive echocardiograms from well-trained experts, beyond simple "point of care ultrasound" evaluations, which can be limited and nonstructured.

Several MRCTs previously studied the potential of iNO for the prevention of BPD in preterm neonates. However, none of these past studies included echocardiography prior to or after randomisation and did not differentiate between preterm infants with or without PH as part of their study design. Mirza *et al.* [113] performed serial echocardiograms in infants born preterm over the first 2 weeks of life and reported variable findings among these infants, which included those with severe PPHN and hypoxaemic respiratory failure, infants reflected delayed pulmonary vascular transition after preterm birth, without extrapulmonary shunt and others with normal estimates of PAP were noted over the first 72–96 h of life (figure 2).

These clinical presentations can be considered as representing different pulmonary vascular phenotypes in infants born preterm, and insights into these phenotypes may be helpful to better understand mechanisms underlying the origins of PH and its pathobiology, the impact of early PVD on the overall clinical course and respiratory outcomes, and specific therapeutic strategies to target differences in disease pathophysiology and outcomes across the lifespan (figure 2) [117–119].

More recently, Arjaans *et al.* [74] performed a prospective, single-centre study of infants born at <30 weeks gestational age to examine the incidence and nature of early PH, and to then characterise subsequent outcomes [74]. The diagnosis of early PH was made according to standard echocardiographic metrics as obtained from studies during the first 3–10 days of postnatal life. Once diagnosed, PH was

further refined and characterised according to three physiological phenotypes, which include classic PPHN, as defined by predominantly right-to-left or bidirectional shunting of blood across the PDA or patent foramen ovale; high-flow PH, as defined by large left-to-right shunting across a nonrestricted PDA; and PH without evidence of a clinically significant shunt. Overall, early PH was diagnosed in 55% of subjects and confirmed past observations that early PH is associated with greater risk of early mortality, greater need for mechanical ventilation, the development of BPD and its severity, and other outcomes [74]. Overall, the high incidence of PH in preterm infants and its association with poor early and late outcomes has major implications for clinical care, research and clinical trial design for infants born preterm and may provide an opportunity for early identification and intervention, which can optimise survival and healthier late outcomes, including BPD-associated PH. We strongly encourage a close collaboration for diagnosis, ongoing care and follow-up among the disciplines, including at least the neonatologist, pulmonologist and cardiologist.

In the previous WSPH congress, PH associated with developmental lung diseases was recognised and emphasised as a distinct and vital group of disorders and was specifically added to the group 3 classification system [1]. Several articles have outlined recommendations to enhance the diagnosis and evaluation of genetic disorders associated with early and severe presentations during the first weeks of life, highlighting the application of modern genetic technologies with clinical care and decision-making in the neonatal ICU setting [120]. Such challenges include how to optimise cardiorespiratory support in critically ill newborns, identification of early clinical markers that increase the likelihood of developmental lung disease-associated PH, the relative roles for genetic studies and consideration of lung biopsy in such cases, and how to optimise communication with families, especially by integrating genetic counselling services, especially in the setting of uncertain outcomes. Typical examples include alveolar capillary dysplasia, the TBX4 syndrome, or surfactant protein abnormalities [75, 112, 121].

CDH is characterised by abnormal development of lung parenchyma and vascular development in association with a defect in the diaphragm due to disruption of distal lung growth and leading to profound hypoxaemic respiratory failure with PPHN [122]. Severe and sustained PH is an important factor that contributes to early mortality, and the need for ECMO and prolonged neonatal ICU care in infants with severe CDH has long been recognised [123]. Early reports demonstrated the potential role of iNO in the management of severe PPHN in CDH, including sustained improvement in oxygenation with reduced extrapulmonary right-to-left shunting; however, subgroup analysis of CDH-associated PH failed to show improved outcomes in the population overall [122]. Partial or poor responsiveness to acute PH-targeted therapy, especially iNO, is related to complex heart–lung interactions and the common contribution of LVDD as being major factors. In an early prospective study, Kinsella and co-workers [124, 125] reported that responsiveness to iNO in term infants with different respiratory diseases associated with PPHN was disease-dependent and enhanced by concurrent enhancement of lung recruitment and ventilator management. Nonresponders to iNO may improve oxygenation and haemodynamics after successful lung recruitment in some infants with CDH, but ventilator strategies are often highly variable between care providers. Importantly, several studies have clearly shown that infants with CDH and PH with echocardiographic evidence of biventricular dysfunction with small LV chambers or LVDD more often required ECMO therapy and had higher mortality beyond the severity of PH alone [125]. As a result, current recommendations for the use of iNO therapy in CDH have emphasised the need for clear echocardiographic evidence of severe PH and RV dysfunction, especially in the presence of predominant right-to-left shunt at the PDA and atrial level, and that right-to-left shunt at the PDA with left-to-right predominant shunt at the atrial level warrants caution due to concerns regarding LV performance and size. Such patients may be especially good candidates with early use of milrinone to further lower PVR, augmenting myocardial contractility and reducing systemic vascular resistance to enhance LV performance beyond the use of iNO alone

Conclusions

Despite major advances in our understanding of disease pathobiology and collaborations with experts in adult PH, improving the care and outcomes of children with PH remains a major challenge due to the unique features of paediatric-specific disorders and the lack of sufficient clinical trial data to provide optimal evidence for therapeutic interventions. Work from this current WSPH paediatric task force highlights recent updates in the field. It emphasises persistent knowledge gaps that need to be addressed to extend survival and enhance our children's and families' quality of life. Ongoing advances in the field include remarkable discoveries in the genetic basis for diverse diseases associated with developmental cardiac and lung diseases, opening perspectives for genetic counselling and precision medicine, Multiple registries worldwide are informing paediatric clinicians on the range of childhood disorders associated with PH, but most importantly, they are providing key data that are leading to the development of risk scores

that will enhance care and research to follow. New prognostic parameters have been identified, and although risk scores for children with PAH or PH still need to be validated, much progress has been made. Unfortunately, PH-targeted drug therapies remain under-studied in paediatric PH, and there is much reliance on observational data and adult experience, primarily with group 1 PAH. This is due to the lack of sufficient MRCTs in childhood PH due to multiple factors, including difficulties in clinical trial design, which have hindered the development of adequate evidence to justify current clinical strategies, especially in infants and young children. As a result, more work is needed to provide more robust bases for consensus recommendations. Greater experience has been garnered regarding the use of a pulmonary to systemic shunt and lung transplantation, but indications and preferences for these therapies are insufficiently defined. Insights into diverse forms of neonatal PH continue to evolve, leading to more specific and pragmatic definitions of pulmonary vascular phenotypes in preterm infants and earlier recognition of genetic causes of developmental lung diseases in various clinical settings. The advantages of serial neonatal echocardiography by highly engaged and collaborative teams of neonatologists and paediatric cardiologists are showing worldwide promise, with early evidence suggesting that high-quality targeted neonatal echocardiography and collaborative PH programs can reduce neonatal morbidities. Thus, many exciting advances in the field have been made since the last WSPH, and ongoing interprofessional collaborations and strategies that bridge pre-clinical and clinical science will continue to improve children's PH outcomes.

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