

IPERTENSIONE POLMONARE: TRA CERTEZZE E DUBBI

Ipertensione arteriosa polmonare in età pediatrica: cosa c'è di nuovo

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2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Historically, the definition of PH in children aged >3 months has been the same as in adults. The definition for PH has now been re-defined to mPAP >20 mmHg in adults as well as in children. The impact of an mPAP 21–24 mmHg on outcomes in children is unknown. However, in the interest of consistency and to facilitate transition from paediatric to adult PH care, it is recommended that the updated definition for PH also be followed in children. No treatment recommendations currently exist for this group of children (mPAP 21–24 mmHg).

Regarding the newly introduced criterion to include $PVR > 2$ WU to identify pre-capillary PH in adults, PVR had previously been included in the definition for PAH in children. In children, blood flows are traditionally indexed assuming 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 of PVR in children is emphasized, and the criterion of pulmonary vascular resistance index $(PVRI) \geq 3$ WU·m² in the definition for PAH in children remains unchanged.⁵⁹⁹



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management

Table 6 Clinical classification of pulmonary hypertension

GROUP 1 Pulmonary arterial hypertension (PAH)

1.1 Idiopathic

TABLE 2 Persistent pulmonary hypertension of the newborn (PPHN) and associated disorders

Idiopathic PPHN	Myocardial dysfunction (asphyxia, infection)
Down syndrome	Structural cardiac diseases
Meconium aspiration syndrome	Hepatic and cerebral arteriovenous malformations
Respiratory distress syndrome	
Transient tachypnoea of the newborn	Associations with other diseases:
Pneumonia/sepsis	Placental dysfunction (pre-eclampsia, chorioamnionitis, maternal hypertension)
Developmental lung disease	Metabolic disease
Peri-natal stress	Maternal drug use or smoking

1.4.3 Portal hypertension

1.4.4 Congenital heart disease

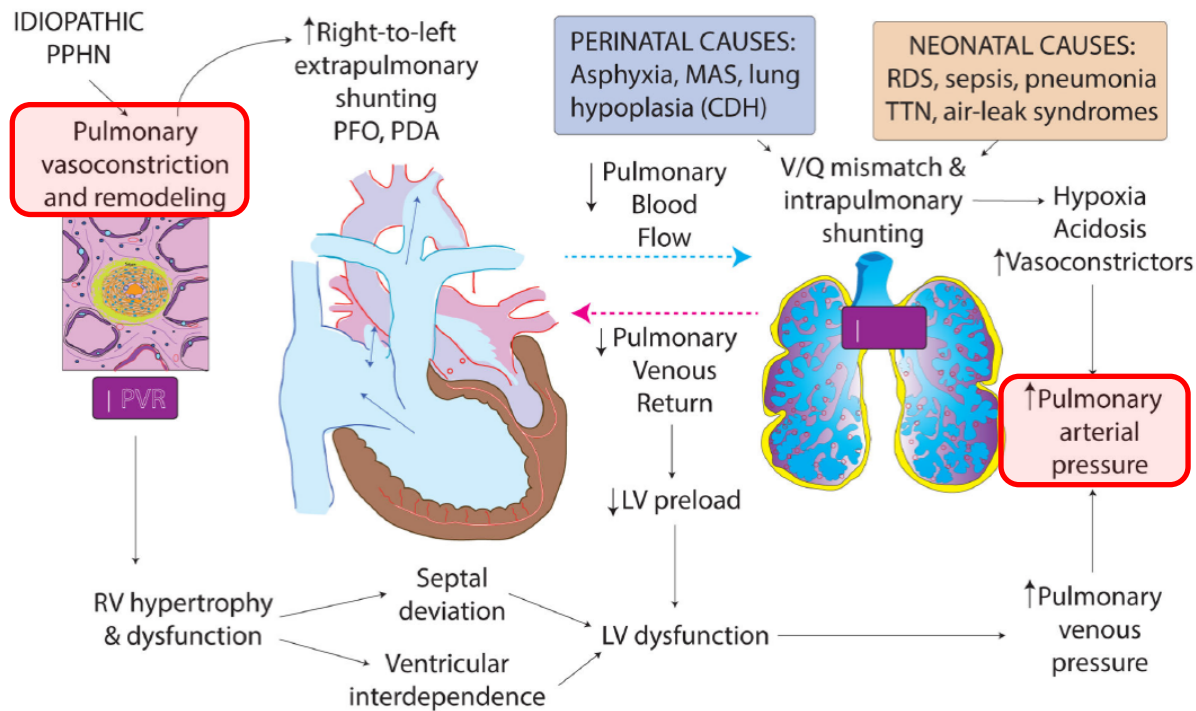
1.4.5 Schistosomiasis

1.5 PAH with features of venous/capillary (PVOD/PCH) involvement

1.6 Persistent PH of the newborn



Pathophysiology and Management of Persistent Pulmonary Hypertension of the Newborn





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TABLE 4 Developmental lung disorders associated with pulmonary hypertension

Bronchopulmonary dysplasia

Congenital diaphragmatic hernia

Down syndrome

Alveolar capillary dysplasia with “misalignment of veins” (FOXF1)

Lung hypoplasia, acinar dysplasia

Surfactant protein abnormalities

Surfactant protein B deficiency

Surfactant protein C deficiency

ABCA3

TTF1/NKX2-1

TBX4

Pulmonary interstitial glycogenesis

Pulmonary alveolar proteinosis

Pulmonary lymphangiectasia

GROUP 3 PH

3.1 Obstructive

3.2 Restrictive

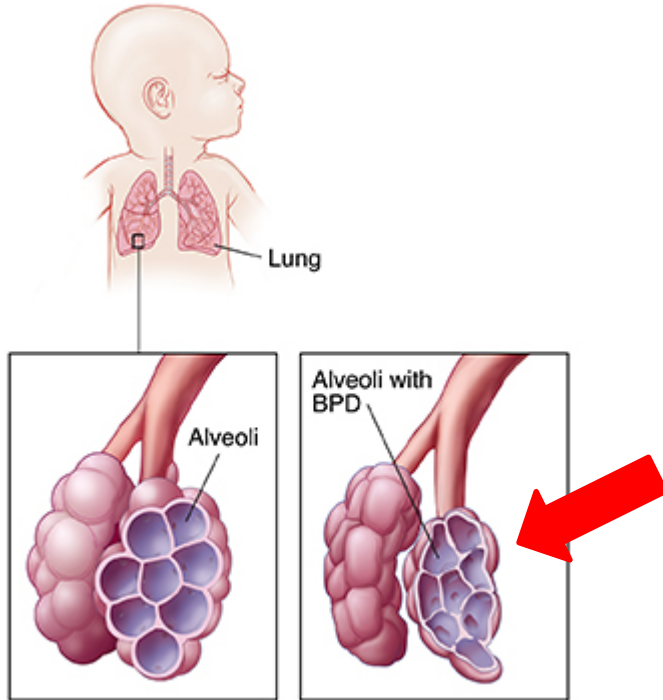
3.3 Lung disease

3.4 Hypoxemia

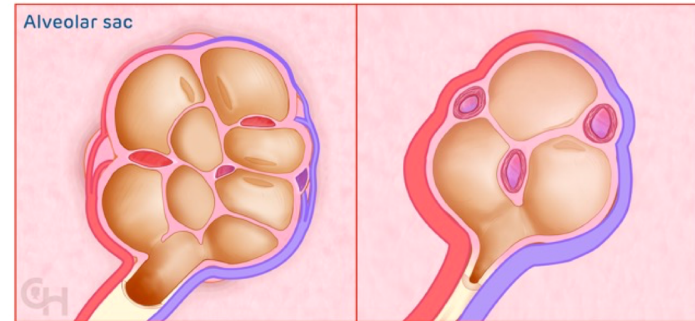
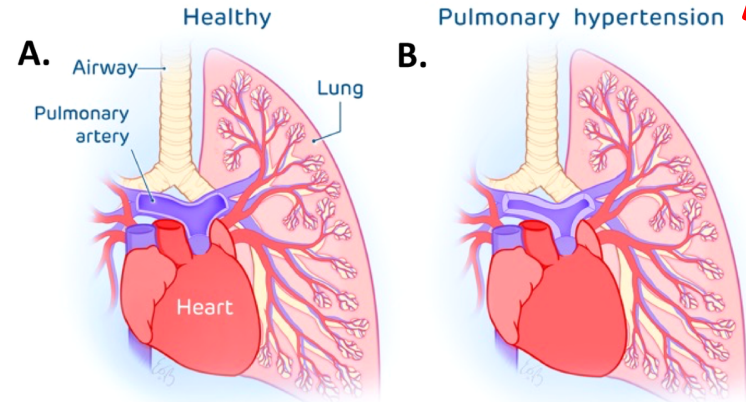
3.5 Hypoxia

3.6 Developmental

Pulmonary Hypertension due to Bronchopulmonary-Dysplasia



Pulmonary hypertension due to BPD



ORIGINAL ARTICLE

Twenty-Year Experience and Outcomes in a National Pediatric Pulmonary Hypertension Service

✉ Andrew Constantine^{1,2,3}, Konstantinos Dimopoulos^{2,3}, Sheila G. Haworth^{1,4†}, Vivek Muthurangu⁴, and Shahin Moledina^{1,4}

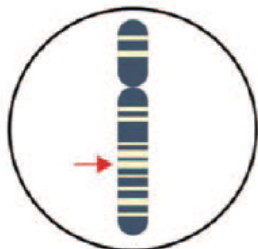
Age group, y	Annual incidence (per 1 million population)					Any PH
	Group 1	Group 2	Group 3	Group 4	Group 5	
0–1	5.89	1.82	15.0	0.09	1.47	24.2
1–5	1.95	0.35	0.95	0.07	0.35	3.67
5–12	1.11	0.20	0.29	0.05	0.34	2.00
12–18	1.08	0.12	0.13	0.06	0.25	1.64
Overall (0–18)	1.56	0.30	1.22	0.06	0.38	3.52
Prevalence (per 1 million population)						
	9.83	1.16	4.93	0.25	1.91	18.1



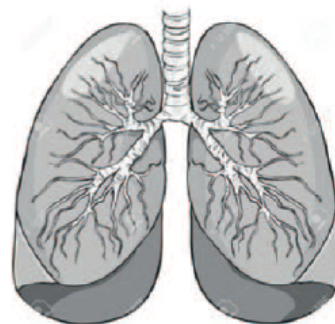
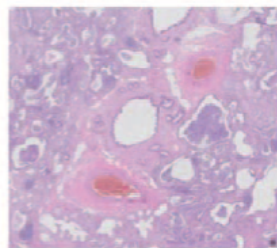
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Chromosome 17
TBX4 gene



Pulmonary arterial hypertension
neonates, children > adults



2002

2016

2019

1996

2013

GRO

3.1

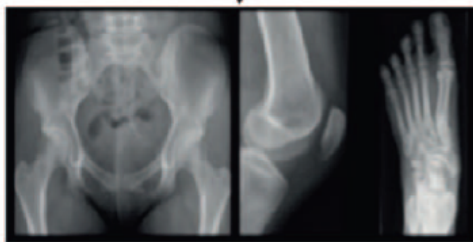
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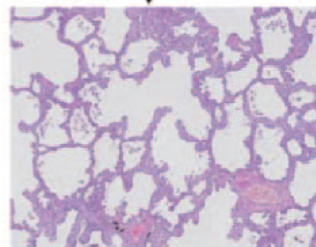
3.4

3.5

3.6



Small patella syndrome



Developmental lung diseases

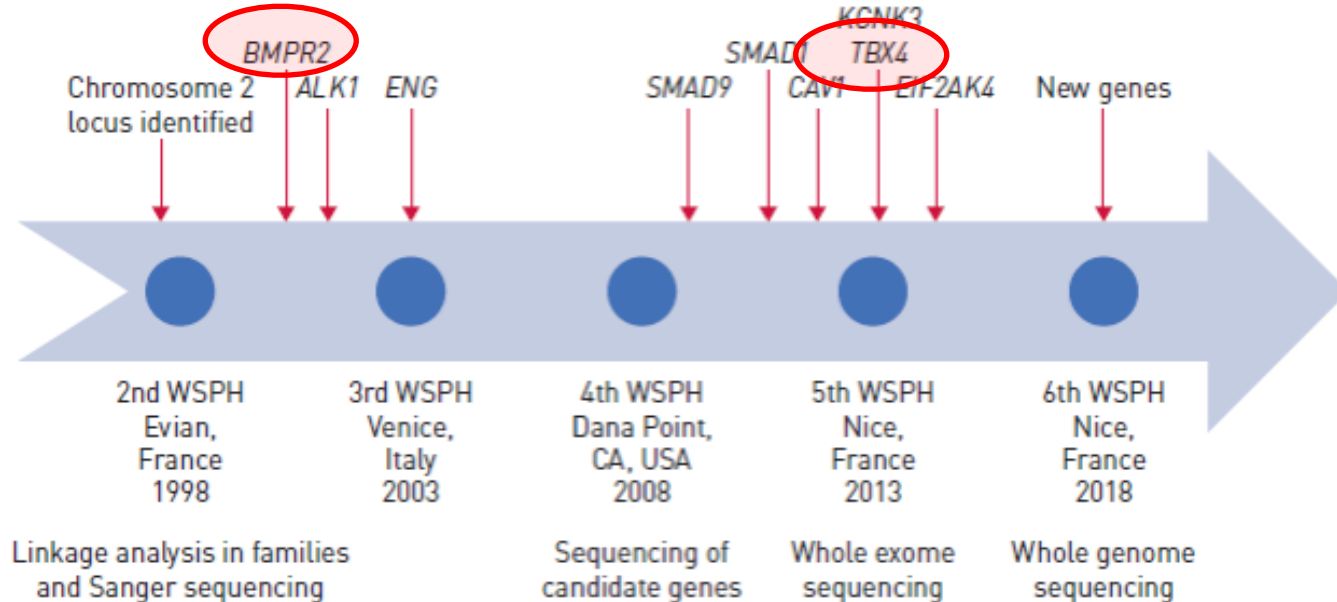
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Role of genetic testing in the diagnosis of PAH

Although a possible genetic origin of PAH was described in the 1950s [100], a new era was opened when pathogenic germline mutations in the *BMPR2* gene were found to be responsible for familial PAH cases in the late 1990s [101, 102]. Since then, several additional genes have been associated with PAH [103]. An international expert panel recently classified 12 genes (*BMPR2*, *ACVRL1*, *ATP13A3*, *CAV1*, *EIF2AK4*, *ENG*, *GDF2*, *KCNK3*, *KDR*, *SMAD9*, *SOX17* and *TBX4*) as having definitive evidence, while three further genes were classified as having moderate evidence (*ABCC8*, *GGCX* and *TET2*) and six genes as having limited evidence supporting a PAH gene-disease relationship [104].

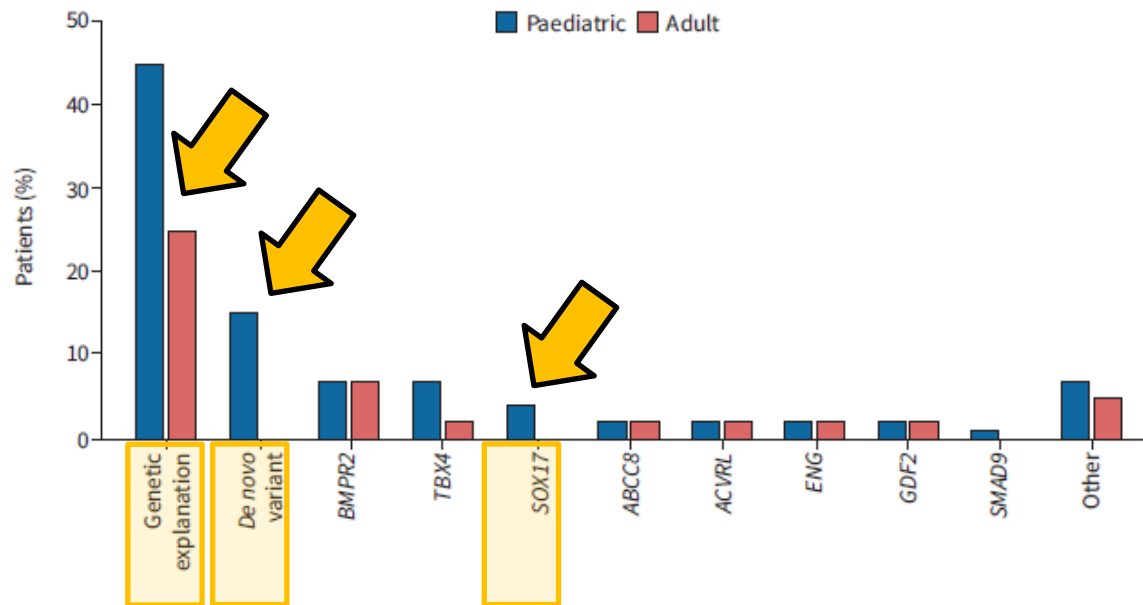
The history of genetic discovery in pulmonary arterial hypertension



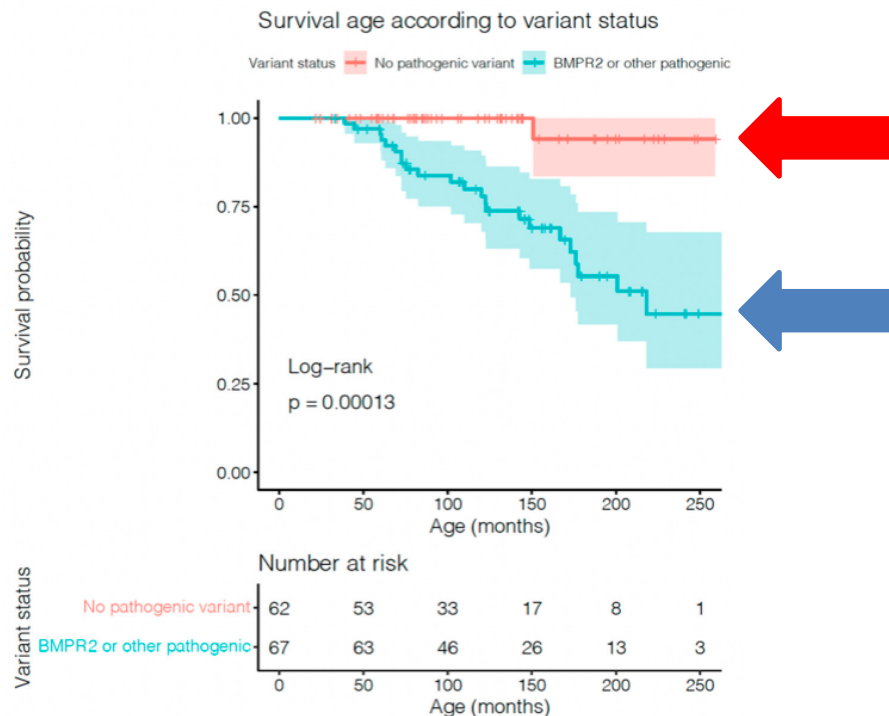


Genetics and precision genomics approaches to pulmonary hypertension

Eric D. Austin¹, Micheala A. Aldred², Mona Alotaibi³, Stefan Gräf⁴, William C. Nichols^{5,6}, Richard C. Trembath⁷ and Wendy K. Chung⁸

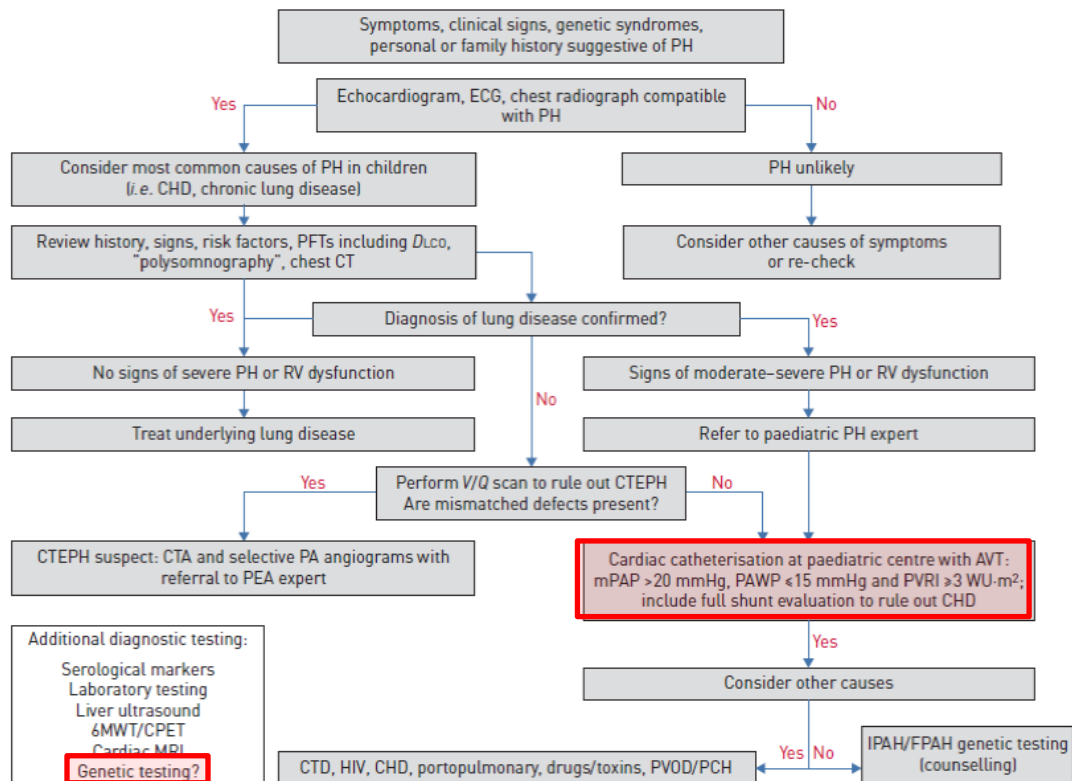


with pathogenic variants ($p = 0.02$). Conclusions: Pathogenic/likely pathogenic genetic variants are prevalent in children with PAH and are related to a worse prognosis irrespective of other recognized risk factors in this population. Combination PAH therapy was associated with superior prognosis in children with pathogenic variants or BMPR2 variants. Therefore, proactive medical therapy should be employed in this population.





Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension



PH classification

	Infant	Child	Adult
1	• PPHN	Complex CHD • IPAH/HPAH • PAH-CHD	Simple CHD • IPAH/HPAH • PAH-CHD • PAH-CTD • PoPH • PAH-HIV
2	• Congenital PVS	• Congenital MS • Cardiomyopathy	• Left heart failure
3	• Developmental lung diseases • Bronchopulmonary dysplasia • Congenital diaphragmatic hernia • Alveolar capillary dysplasia	• Trisomy 21 • chILD • Hypoventilation syndrome	• COPD • ILD
4	• Congenital PS	• Congenital PS	• CTEPH
5		• Metabolic disorders	• Haematologic diseases • Systemic diseases

Comorbidities

• Congenital malformations	• Chromosomal abnormalities • Syndromic features	• Diabetes • Hypertension • Heart failure • Renal failure
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Risk factors for outcome

• Respiratory support • Steroids • Suprasystemic PH • ASD/VSD • Necrotizing enterocolitis	• Risk assessment tool	• Risk assessment tool
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Diagnosis

• Echocardiography • RHC?	• RHC+AVT* • Diagnostic algorithm	• RHC+AVT* • Diagnostic algorithm
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Therapy

• Optimize respiratory support • Nutritional support	• GORD treatment • Inhaled NO, PAH drugs	• Treatment algorithm	• Treatment algorithm
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Evidence

• Extremely limited	• +/- • Cohort studies	• +++ • RCTs
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ESC

European Society
of Cardiology

European Heart Journal (2022) 00, 1–114
<https://doi.org/10.1093/eurheartj/ehac237>

ESC/ERS GUIDELINES

Embracing the challenges of neonatal
pulmonary hypertension

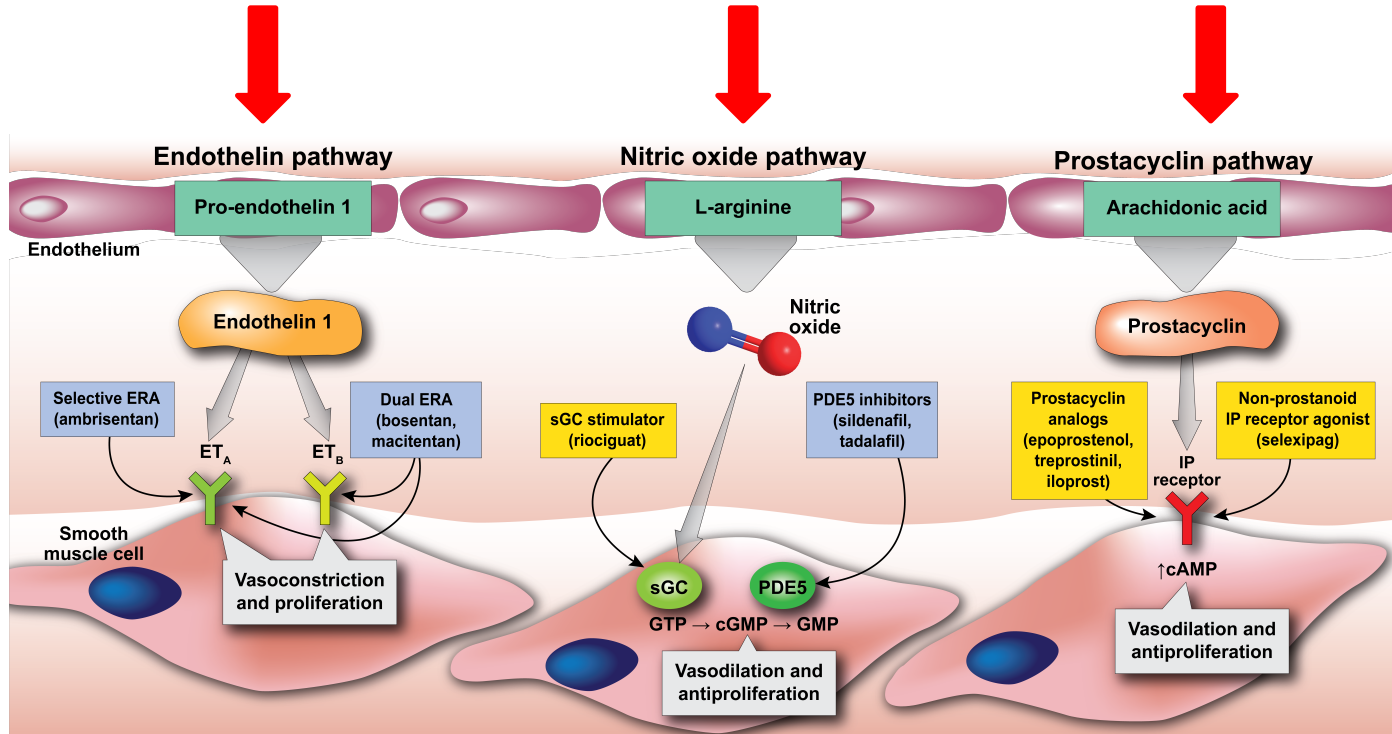
Dunbar Ivy¹, Erika B. Rosenzweig², Steven H. Abman³,
Johannes Menno Douwes⁴, Alessandra Manes⁵ and Rolf M.F.

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

PAH or operability in children with CHD. Since RHC in children with PH may be associated with major complications (in 1–3% of cases, especially in young infants and those in worse clinical condition), risks and benefits have to be balanced in the individual child.⁶⁰⁵ Heart catheterization in children with PAH should be exclusively performed in experienced paediatric PH centres. Indications for repeated RHC in children with PH are currently not well defined.

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Molecular targets of approved PAH drug therapies



Lau, E. M. T. et al. (2017) Epidemiology and treatment of pulmonary arterial hypertension

Nat. Rev. Cardiol. doi:10.1038/nrcardio.2017.84



Embracing the challenges of neonatal and paediatric pulmonary hypertension

Dunbar Ivy ¹, Erika B. Rosenzweig², Steven H. Abman ³, Maurice Beghetti⁴, Damien Bonnet ⁵, Johannes Menno Douwes⁴, Alessandra Manes⁴ and Rolf M.F. Berger ⁶

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

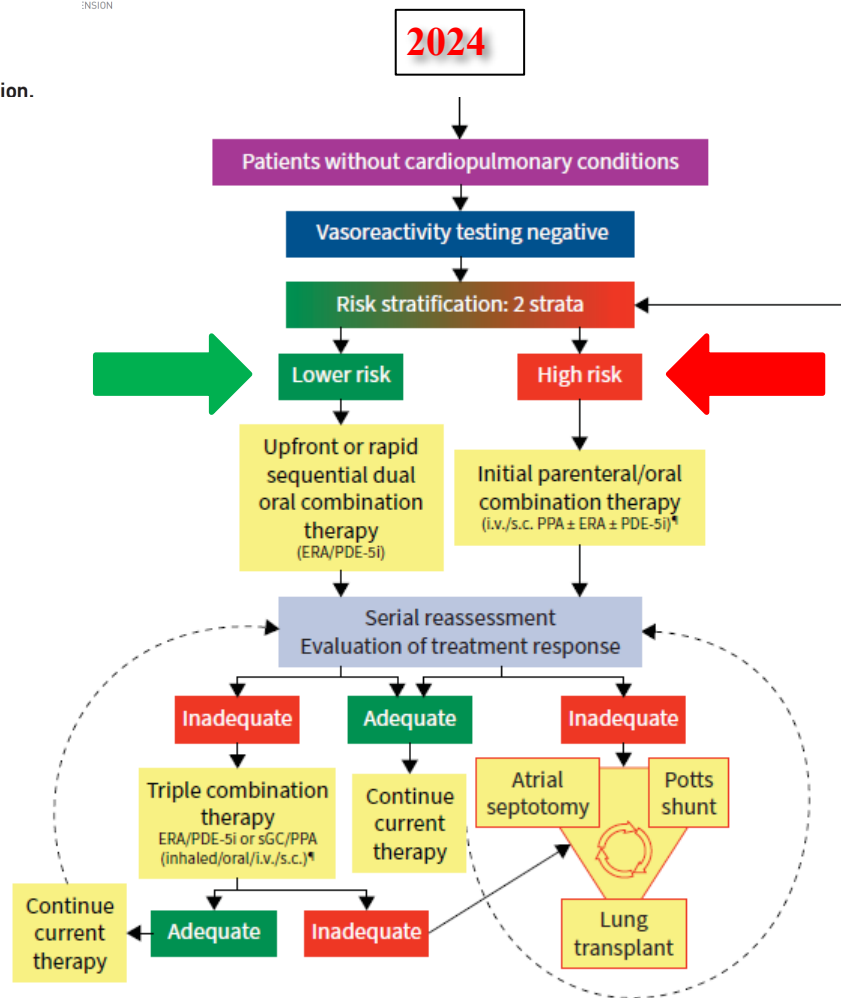
	EMA approval	FDA approval	Comments
<u>PDE-5i</u>			
Sildenafil	Yes	Yes	EMA: age 1–17 years FDA: age 1–17 years
Tadalafil	Yes		EMA: age >2 years
<u>sGC stimulator</u>			
Riociguat	Yes		EMA: >50 kg
<u>ERA</u>			
Bosentan	Yes	Yes	FDA: age >3 years EMA: age >1 year
Ambrisentan	Yes		EMA: age 8–18 years
Macitentan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



Embracing the challenges of neonatal and paediatric
pulmonary hypertension



**hypertension: updates on definition,
classification, diagnostics and**





Embracing the challenges of neonatal and paediatric pulmonary hypertension

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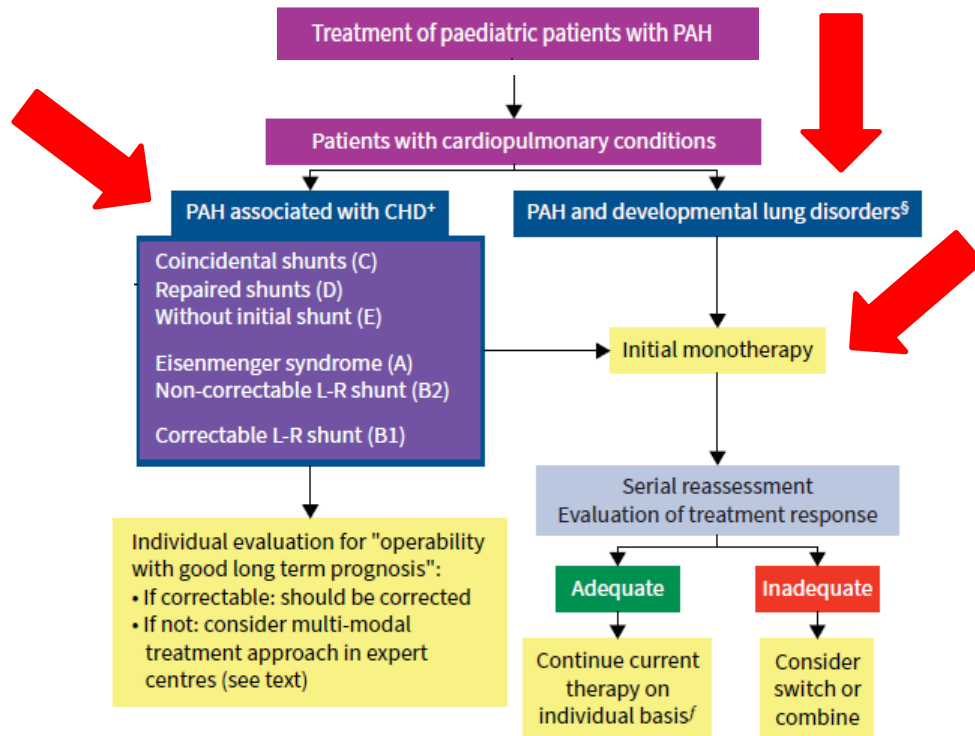
2024

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 _{vO₂} %	≥ 65	< 65
Acute response Sitbon criteria	Yes	
Cardiac MRI		
RVEF %	≥ 44	< 44
RVMI g·m ⁻²	≤ 80	> 80



2024



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Infants		
It is recommended to screen infants with bronchopulmonary dysplasia for PH ^{628,629}	I	B
In infants with (or at risk of) bronchopulmonary dysplasia and PH, treating lung disease—including hypoxia, aspiration, and structural airway disease—and optimizing respiratory support is recommended before initiating PAH therapy ⁶³⁰	I	B



ORIGINAL ARTICLE

Twenty-Year Experience and Outcomes in a National Pediatric Pulmonary Hypertension Service

Andrew Constantine^{1,2,3}, Konstantinos Dimopoulos^{2,3}, Sheila G. Haworth^{1,4†}, Vivek Muthurangu⁴, and Shahin Moledina^{1,4}

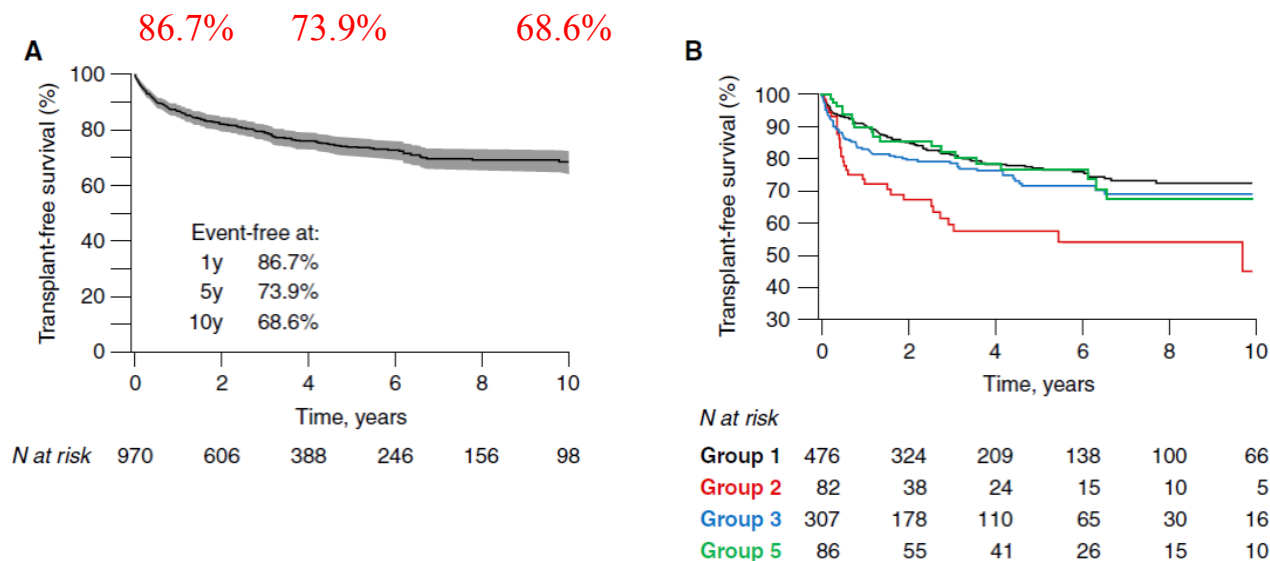


Figure 3. Kaplan-Meier survival curves in children with pulmonary hypertension, (A) in the overall cohort and (B) for the different pulmonary hypertension groups. The numbers below the horizontal axis represent the number of patients at risk.

Enhancing Drug Development for Paediatric Pulmonary Hypertension—An Integrative Perspective

Steven H. Abman¹ | Sylvia M. Nikkhor² | Rolf M. F. Berger³ | María Jesús del Cerro⁴ | Eric D. Amdur⁵ | Maurice Baggett⁶ | Dunbar Ivy⁷ | Megan Griffiths⁸ | Anne Hilgendorf⁹ | Steven H. Kawut¹⁰ | Usha S. Krishnan¹¹ | Mary P. Mullen¹² | Shahin Mohtased¹³ | Bernard Thebaud¹⁴ | Norman Stockbridge¹⁵

Children are not simply “small adults,” and similarity of certain features of the disease does not necessarily align with the adult experience, see Table 1. PAH presents a significant challenge in both paediatric and adult populations, with distinct differences often related to the underlying developmental biology and timing of disease onset, but also similarities in pathophysiology, disease progression, and patient characteristics as described in

TABLE 1 | Comparative features of PAH in paediatric and adult populations.

Aspect	Adult population	Paediatric population
Prominence of PH groups	Majority have idiopathic/hereditary PAH; more cases related to CTD [11, 12].	Majority have idiopathic/hereditary PAH; larger proportion with CHD-related PH [6, 11].
Symptoms	Dyspnoea on exertion, lower extremity oedema, light headedness, chest pressure and heart failure more frequent [11, 12].	Dyspnoea on exertion most frequent, syncope more common [11, 13].
Haemodynamics	Severe elevations in PVR and PAP, more heart failure [7].	Severe elevations in PVR and PAP, less heart failure [11, 13].
Life expectancy	5-year survival rates based on contemporary registry data of approximately 84% in incident cases, despite modern treatment approaches [14].	Similar poor life expectancy with reported 5-year overall survival of 74% [3, 4].

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Despite the availability of drug are used off-label in children between paediatric and adult supported by anecdotal experience is evidenced by data showing registry received PAH-targeted standard of care [41]. However, creates challenges for clinicians, caregivers, and physicians making studies that could restrict access

The decline in drug trials for paediatric populations can be attributed to several factors, including regulatory challenges that complicate trial design, and heightened ethical considerations

Furthermore, there is often a significant delay between the approval of new treatments for adults and the initiation of paediatric efficacy trials, leading to widespread off-label use of adult therapies in children. This situation can lead to a lack of equipoise among clinicians regarding the standard of care, complicating the justification for placebo-controlled trials. Trial design also faces difficulties, as randomized, double-blind, controlled investigations, which are the gold standard for establishing evidence of effectiveness, may not be practical and ethical. Concerns from parents and caregivers about randomization into placebo groups—especially when the drug is approved in adults—and the option at some point in the study to receive the treatment can further complicate recruitment and retention of subjects in trials. Lastly, clinical endpoints must be

trials presents difficulty [4–6]. This indicates the rarity of the relation and the es, infants, and n age, physical ad recommen-

Take-at-home message ...

Despite many unique characteristics, children with PH are often assessed and managed based on adult PH guidelines. The WSPH Paediatric Task Force had an opportunity to further highlight some of the inherent differences between children and adults with PH

The current 2024 7th WSPH classification incorporates the growing population of children with developmental lung diseases, such as BPD and CDH, complex CHD, and novel mutations.

Children with PH should be evaluated and treated in comprehensive, multidisciplinary clinics at specialized pediatric centers

The field of paediatric PH still requires future paediatric-specific clinical trials in order to develop specific treatment strategies and clinical end-points for children with PH.