

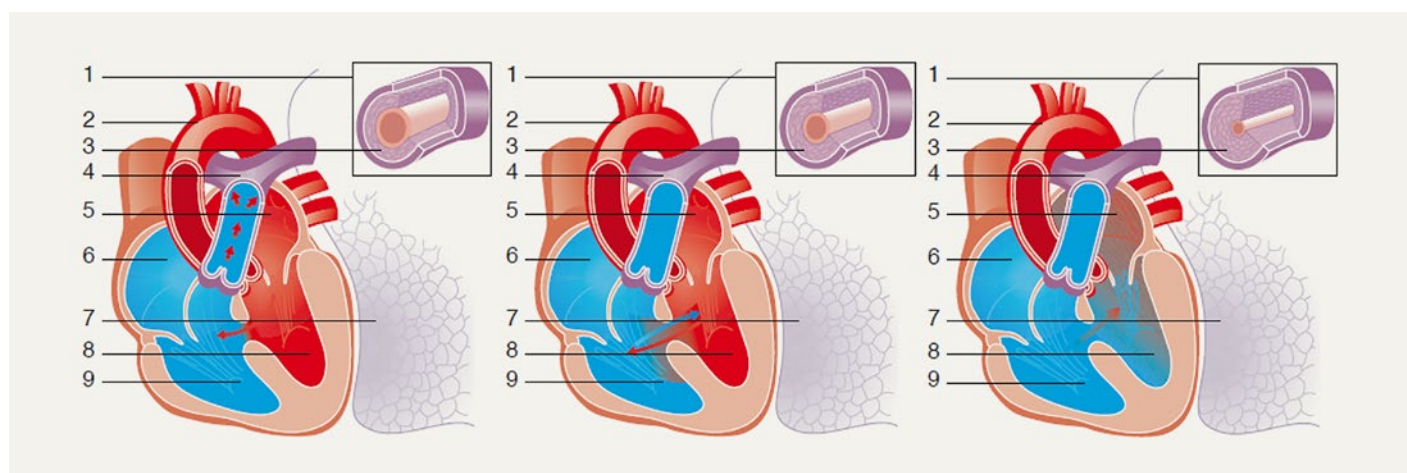


Figure 1: Evolution of a systemic-to-pulmonary shunt towards Eisenmenger syndrome. 1. Pulmonary arteriole. 2. aorta. 3. Media. 4. Pulmonary artery. 5. left atrium. 6. right atrium. 7. lung. 8. left ventricle. 9. right ventricle. Reproduced with permission from [6].

Overview of the current definition, classification, diagnosis strategy and treatment

Paediatric pulmonary hypertension

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Introduction

Children can present at any age with pulmonary hypertension. Aetiologies of paediatric pulmonary hypertension are different from those of adults, with a predominance of idiopathic pulmonary arterial hypertension (iPAH), PAH associated with congenital heart disease (PAH-CHD) and developmental lung disease. Older children with iPAH, despite specific differences, resemble adults with PAH. With improved care, many congenital heart disease patients survive into adulthood. Specialists in adult congenital heart disease will increasingly be required to look after patients with PAH-CHD. Pulmonary hypertension owing to developmental lung disease presents in neonates, and its impact on the immature and developing lung makes its presentation, diagnosis, response to therapy and outcome quite different from pulmonary hypertension associated with adult lung disease.

The management of children with PAH remains challenging owing to the lack of studies on the efficacy of targeted therapy in paediatric

rics, and treatment is mainly based on small studies, data extrapolation from adult studies and international expert recommendations. Targeted therapies can slow clinical worsening in the various forms of paediatric PAH, but curative therapy remains elusive. The use of targeted therapies in children with developmental lung disease is debatable and lacks evidence.

In this article, we provide an overview of the current definition, classification, diagnosis strategy and treatment of pulmonary hypertension in children, with a special focus on pulmonary hypertension associated with congenital heart disease or due to developmental lung disease.

Definition, epidemiology, classification

The definition of pulmonary hypertension was revised in 2018 during the 6th World Symposium on pulmonary hypertension in Nice (France), and is defined as mean pulmonary artery pressure (mPAP) >20 mm Hg measured

by right heart catheterisation [1]. This value should be used only after 3 months of age, because of the normal transition from fetal iso-systemic PAP to normal values in the first few weeks of life. Moreover, pulmonary vascular resistance (PVR) is often used in paediatrics, in order to assess the presence of pulmonary vascular disease (PVD), as defined by indexed PVR (PVRi) ≥ 3 WU·m² [2].

The estimated incidence of paediatric pulmonary hypertension is 4–10 cases per million children per year, with a prevalence of 20–40 cases per million in Europe [3, 4].

Pulmonary hypertension classification has undergone several revisions, adapting to the ever-evolving understanding of the disease. Table 1 summarises the current classification, and highlights the categories of interest for paediatric pulmonary hypertension.

Congenital heart disease is one of the main aetiologies of paediatric pulmonary hypertension, and deserves specific consideration. Particular groups of congenital heart disease patients are at risk of developing pulmonary

hypertension. Pulmonary artery pressure can be raised by increased pulmonary blood flow, as in left-to-right shunt lesions, causing precapillary PAH. It can also be due to increased left atrial pressure, as in left-sided heart disease provoking postcapillary PH (PH-LHD). In both cases, an increase in PVR secondary to anatomical and functional changes in the pulmonary vascular bed can aggravate PH. The aetiology of PH can also be mixed, complicating diagnosis and management of PAH-CHD [5].

Eisenmenger syndrome is the final and irreversible stage of PAH-CHD when PVR is higher than systemic vascular resistance leading to shunt reversal and cyanosis (fig. 1) [6].

In left-sided heart disease, PVD can develop on top of the passive transmission of the left atrial pressure to the pulmonary vasculature. This situation is referred to as combined post- and precapillary pulmonary hypertension (CpcPH), when mPAP increases in excess of the elevation of the pulmonary artery wedge pressure, and occurs in about 20% of PH-LHD [7, 8].

Pulmonary vascular disease in single ventricle physiology had until recently been excluded from the pulmonary hypertension classification because most Fontan patients usually do not fulfill the definition of pulmonary hypertension with a mPAP >20–25 mm Hg. However, PVD in the Fontan circulation significantly impacts survival. The revised classification

placed single ventricle physiology in group 5 (pulmonary hypertension with unclear and/or multifactorial mechanisms), alongside complex heart diseases associated with congenital anomalies of the pulmonary vasculature (such as segmental pulmonary hypertension). Although haemodynamic evaluation before Fontan completion is performed in most centres, a proportion of patients will present with “failing Fontan”. Fontan failure can be due to several different mechanisms, including single-ventricle systolic or diastolic dysfunction, obstruction in the venous or arterial pathway, atrioventricular valve regurgitation, but more importantly, PVD. Indeed, without a subpulmonary ventricle, PVR plays a major role in regulating pulmonary blood flow, and even low grade of PVD can impact prognosis [9].

Diagnosis

A thorough diagnostic workup, illustrated in figure 2, is necessary in order to classify pulmonary hypertension, assess its severity and start appropriate treatment [10]. Idiopathic PAH is a diagnosis of exclusion, and ruling out all other possible causes of pulmonary hypertension is paramount. Laboratory studies aiming to diagnose other causes of pulmonary hypertension (connective tissue disease, human immunodeficiency virus infection, liver disease, hypercoagulability, and others) should

be performed. Genetic testing should be considered in all cases of iPAH.

Right heart catheterisation generally requires general anaesthesia in children, which is not without risks, especially among the most severe cases, with a 5.9% rate of reported complications, including 0.6% deaths [11]. Therefore, it should be performed at paediatric pulmonary hypertension centres, with an experienced anaesthetic team and overnight intensive care haemodynamic monitoring. In very severe cases, the option to start pulmonary vasodilators and perform cardiac catheterisation after the patient has stabilised is chosen by some centres. Acute vasodilator testing should be performed in iPAH and heritable PAH to identify the responders who would benefit from calcium channel blocker therapy. It is also done in a subset of PAH-CHD patients with some increase of PVR, to assess operability. In most cases, PAH in children is characterised by a preserved cardiac index and right atrial pressure despite elevated PVRi, with better preservation of right ventricular function than in adults [12].

Treatment

We review here treatment for PAH patients, as illustrated in figure 3. Treatment of other PH groups of interest in paediatrics are detailed under “Special considerations” below.

Table 1:

Updated clinical classification of pulmonary hypertension

1 PAH	Examples, subclassifications
1.1 Idiopathic PAH 1.2 Heritable PAH 1.3 Drug- and toxin induced PAH 1.4 PAH associated with 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH long-term responders to calcium channel blockers 1.6 PAH with overt features of venous/capillaries involvement 1.7 Persistent PH of the newborn syndrome	Systemic-to-pulmonary shunt lesions (VSD, PDA, AVSD, Truncus, ASD, TGA/VSD) A. Eisenmenger's syndrome B. PAH associated with prevalent systemic to pulmonary shunt C. PAH with small/coincidental defects D. PAH after defect correction
2 PH due to left heart disease 2.1 PH due to heart failure with preserved LVEF 2.1 PH due to heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH	PV stenosis, cor triatriatum, obstructed TAPVD, mitral/aortic stenosis, coarctation
3 PH due to lung diseases and/or hypoxia 3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders	BPD, CDH, Down syndrome, lung hypoplasia, surfactant protein abnormalities, ...
4 PH due to pulmonary artery obstructions (including chronic thromboembolic PH)	
5 PH with unclear and/or multifactorial mechanisms	
5.1 Haematological disorders 5.2 Systemic and metabolic disorders 5.3 Others 5.4 Complex congenital heart disease	Segmental PH, Scimitar syndrome, single ventricle physiology

ASD: atrial septal defect; AVSD: atrioventricular septal defect; BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; LVEF: left ventricular ejection fraction; PDA: patent ductus arteriosus; PV: pulmonary veins; TAPVD: total anomalous pulmonary venous drainage; TGA: transposition of the great arteries; VSD: ventricular septal defect. Adapted from [1].

Review article

General measures that are currently recommended for paediatric patients with PAH include ensuring that all immunisations (of the patient and the family) are up to date, including influenza, pneumococcal and more recently COVID-19 vaccinations, avoidance of dehydration, and encouragement to maintain moderate physical activity. Diuretics are recommended in the setting of right heart failure and fluid retention. Oxygen therapy may be considered in patients with severe hypoxaemia at rest or during exercise. Oral anticoagulants are of unclear benefit, and usually reserved for patients on epoprostenol infusion, because of the additional risk of catheter-associated thrombosis. Iron deficiency, even without anaemia, is associated with a higher risk of adverse outcome and correcting iron deficiency should be integrated into follow up [13].

High dose calcium channel blockers are reserved for the subset of iPAH and hereditary

PAH responders to acute vasoreactivity testing, and efficacy should be assessed by a repeat right heart catheterisation after 3 months. Calcium channel blockers are contraindicated in children with right ventricular failure (because of their negative inotropic effect) and in PAH-CHD, as they may cause significant peripheral vasodilation, increased right to left shunting (hypoxia), syncope and sudden cardiac death.

Specific therapies currently available target three pathophysiological pathways implicated in pathogenesis of PAH (endothelin, NO and prostacyclin) [14].

Endothelin receptor antagonists

Bosentan is a dual endothelin-1 receptor antagonist approved since 2001 for the treatment of PAH [15]. The BREATHE-5 study in adult Eisenmenger patients showed safety and efficacy of bosentan therapy in improving haemo-

dynamics and exercise capacity after 16 weeks of treatment [16]. Bosentan has been used off-label in paediatric PAH patients with reported shortterm benefits on functional class and haemodynamics [17, 18].

Safety studies FUTURE-1 [19] and FUTURE-2 [20] tested a paediatric formulation of bosentan and concluded that a dose of 2 mg/kg twice daily was well tolerated, safe and appropriate in children with PAH. This paediatric formulation is approved in numerous countries, including Australia, the US and Europe.

Macitentan is a newer dual endothelin receptor antagonist, developed by modifying the structure of bosentan with the view to improve drug efficacy and safety, and has shown efficacy in adult PAH patients [21]. Interestingly, the MAESTRO study performed in Eisenmenger syndrome patients failed to show superiority of macitentan over placebo in

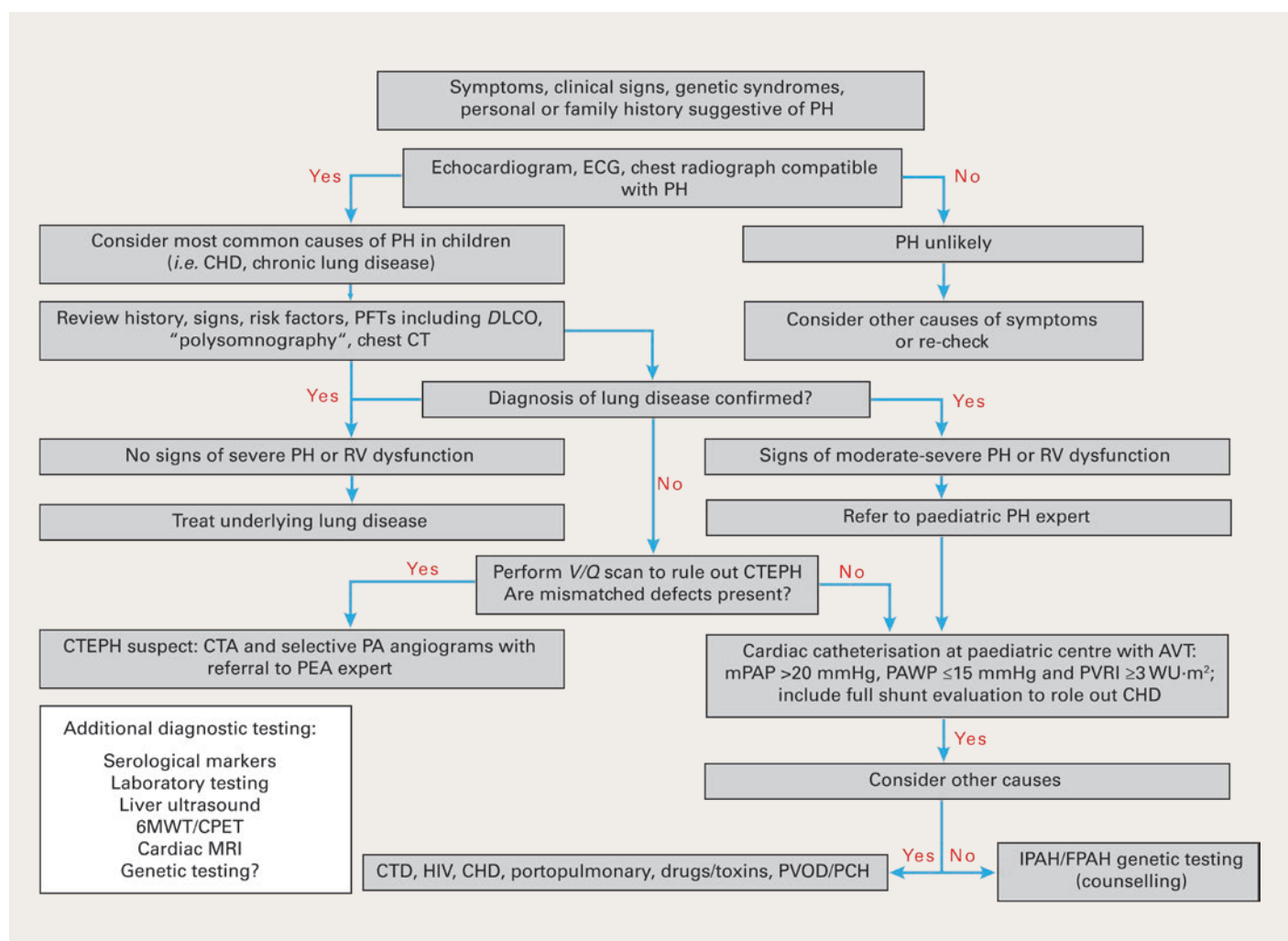


Figure 2: Diagnostic algorithm for pulmonary hypertension in children.

AVT: acute vasodilator testing; CHD: congenital heart disease; CPET: cardiopulmonary exercise test; CTA: CT angiography; CTEPH: chronic thromboembolic PH; CTD: connective tissue disease; DLCO: diffusing capacity of the lung to carbon monoxide; FPAH: familial PAH; PAWP: pulmonary arterial wedge pressure; PCH: pulmonary capillary haemangiomatosis; PEA: pulmonary endarterectomy; PFT: pulmonary function test; PVOD: pulmonary veno-occlusive disease; RV: right ventricle; V/Q: ventilation/perfusion; 6MWT: 6-minute walk test. reproduced with permission from [2].

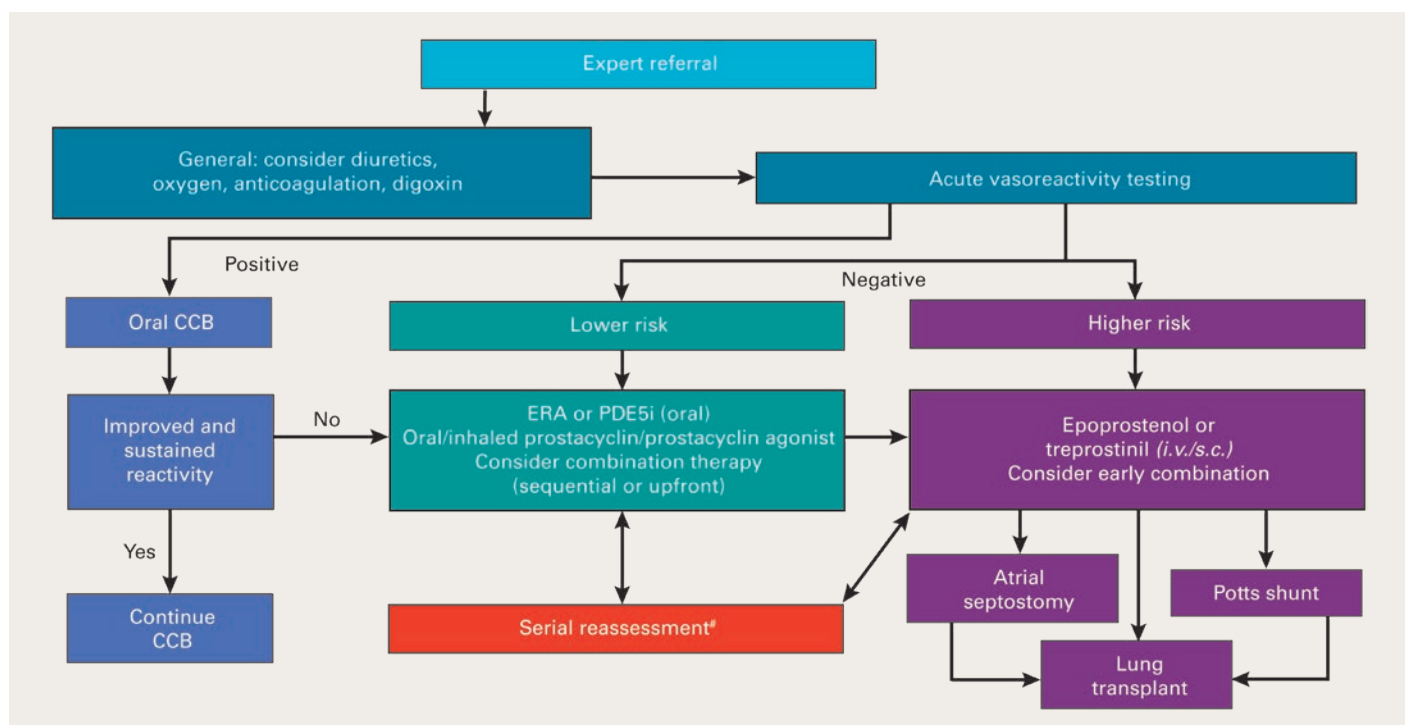


Figure 3: Paediatric idiopathic/familial pulmonary arterial hypertension treatment algorithm. CCB: calcium channel blocker; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor. #: deterioration or not meeting treatment goals. Reproduced with permission from [2].

improving exercise capacity after 16 weeks of treatment, partly explained by the unexpected improvement in exercise capacity in the placebo arm [22]. A phase III trial on the use of macitentan in children aged 2–17 years with PAH is ongoing (TOMORROW study; NCT02932410).

Phosphodiesterase type 5 inhibitors and guanylate cyclase inhibitors

The NO-cyclic guanosine monophosphate (NO-cGMP) pathway is involved in vascular relaxation, inhibition of leucocyte recruitment and inhibition of platelet aggregation. Phosphodiesterase type 5 inhibitors (PDE-5i) enhance the NO-cGMP pathway by slowing cGMP degradation. Several small-scale studies in children with iPAH and PAH-CHD reported an improvement of exercise capacity and haemodynamics by treatment with sildenafil, a selective PDE-5i [23–25].

The randomised controlled STARTS-1 trial in treatment-naïve children with PAH demonstrated a benefit with a medium and high dose of sildenafil versus placebo on peak oxygen consumption, functional capacity and haemodynamics [26]. An unexpected increased risk for mortality was found in the high-dose sildenafil group in the extension study (STARTS-2), prompting a Food and Drug Administration (FDA) “black box” warning against the chronic use of sildenafil in children with PH, which was then clarified, and sildenafil has continued to be used follow-

ing experts’ opinion. After reviewing the data, the European Medicines Agency (EMA) recommended the following doses of sildenafil: 10 mg three times a day for children <20 kg, and 20 mg three times a day for children >20 kg.

Tadalafil is a longer acting PDE-5i, requiring once-daily dosing. Early paediatric experience demonstrated the safety and potential efficacy on haemodynamics and walking distance of tadalafil in children with PAH [27, 28]. Riociguat, a soluble guanylate cyclase stimulator acting in synergy with endogenous NO and also independently, has been approved for the treatment of PAH in adults since 2014 and improves exercise capacity, haemodynamics, and functional class. Trials evaluating safety and efficacy of riociguat in paediatric patients are ongoing.

Prostacyclin analogues and prostacyclin receptor agonists

Prostacyclin is produced in the vascular endothelial cells and induces relaxation and inhibits the growth of vascular smooth muscle cells. Intravenous epoprostenol was one of the only available targeted therapies in the 1990s, and improved survival in children with iPAH and PAH-CHD [29, 30]. Because of its route of administration and potential complications, epoprostenol is unattractive for first-line therapy but remains the gold standard for severe, WHO functional class IV, pulmonary hypertension.

Treprostinil, a stable analogue of epoprostenol that can be administered subcutaneously or intravenously, could represent an alternative strategy, although the non-inferiority to epoprostenol in PAH treatment remains to be proven [31–33].

Data are pending regarding the safety and efficacy of selexipag, a novel oral selective agonist of the prostacyclin receptor, in paediatric and Eisenmenger syndrome patients. A paediatric randomised controlled trial evaluating selexipag as add-on treatment to standard of care in children with PAH is underway (SALTO, NCT 04175600).

Combination therapy

Upfront combination therapy might permit to achieve a better control of the disease than the previous strategy of sequential combination, which consisted of the addition of a second or a third drug in the case of an unsatisfactory effect or clinical deterioration [34–36]. In children, the majority of patients are still started on monotherapy, as shown by data from the international TOPP registry [37]. However, recent evidence indicates that combination therapy improves outcome for paediatric PAH [38] and is indeed currently recommended by experts.

Lung transplant and palliative interventions

The ultimate palliation for pulmonary hypertension is lung transplant, or heart and lung transplant / lung transplant associated with

corrective cardiac surgery in the case of PAH-CHD. However, shortage of donor organs, waiting list mortality and median survival in children following lung transplantation have limited the long-term success of this procedure [39]. Current 5-year survival rates after paediatric lung transplantation is 64% for iPAH and 43% for non-idiopathic PAH [39]. Surgical or interventional strategies to delay the need for transplantation (atrial septostomy, reverse Potts shunt) are increasingly performed in severe cases of pulmonary hypertension [40, 41]. A recent retrospective study using an international paediatric registry found a 5-year outcome in 110 children who underwent reverse Potts shunt comparable to the outcome of primary lung transplantation for pulmonary hypertension [42]. In the French-speaking part of Switzerland, six patients with PAH underwent lung transplantation since 2011, including only one pediatric patient (unpublished data). Data from Zurich are similar, with 11 PAH patients transplanted since 2011.

Psychosocial and economic considerations

Pulmonary hypertension is a severe condition, with many psychosocial implications for the patients and their families. Specific therapies are costly, although usually reimbursed by health insurance in Switzerland. Early involvement of social workers, mental health and palliative care teams can help patients and their families dealing with the psychosocial burden of pulmonary hypertension. Collaboration with the paediatrician is important for dealing with all the different aspects of a chronic disease on a growing child, with cardiology follow up in the PAH expert centre every 3–6 months.

Special considerations

Pulmonary arterial hypertension associated with congenital heart disease

When diagnosed early enough, corrective surgery or percutaneous closure of the cardiac shunt is the best way to prevent PAH development. For example, ventricular septal defects and patent ductus arteriosus should be closed before the age of 6–12 months, atrioventricular septal defects at 3–6 months, and truncus arteriosus before the age of 3 months [43]. When diagnosed later, patients should undergo evaluation and be placed in one of the PAH-CHD categories and treated accordingly. If categorised as PAH associated with a prevalent systemic-to-pulmonary shunt, operability should be determined based on haemodynamic criteria, and case-by-case decision-making in expert centres for borderline cases.

Pulmonary hypertension due to left heart disease

Management of PH-LHD predominantly involves treatment of the underlying left heart disease. Reversibility or improvement of pulmonary hypertension after successful causal treatment can be expected in the majority of cases [44–46]. However, a subset of patients display residual pulmonary hypertension even after successful reduction of left atrial pressure, challenging the historical concept that PH-LHD was almost always reversible [47]. Precise haemodynamic data before and after intervention could help identify patients at increased risk of residual pulmonary hypertension. Most studies on specific vasodilators in PH-LHD have been disappointing, at best failing to show a clear benefit [48–52], or even reporting a clinical worsening [53–55]. This can be explained by the potential deleterious effect of pulmonary vasodilation in patients with left sided heart failure, leading to increased pulmonary venous congestion and a worsening clinical scenario. Although not currently recommended owing to lack of evidence, use of pulmonary vasodilator therapies is appealing in the category of patients with CpcPH, and efforts should be made in designing trials including those patients.

Failing Fontan

As discussed previously, numerous manifestations of failing Fontan are a consequence of increased PVR, and treatment with pulmonary vasodilators makes intuitive sense. However, the paediatric task force of the 6th World Symposium on Pulmonary Hypertension does not support the use of pulmonary vasodilators in the Fontan population because of insufficient data on safety and efficacy [2]. Published data have shown contrasting results so far [56–60]. In our experience, pulmonary vasodilators may be helpful in the immediate postoperative period and for a short period of time, for example in the case of elevated central venous pressure and persisting pleural effusion. Further studies are needed to help determine if Fontan patients might benefit from targeted therapies, and if this is the case, select the appropriate patients, the timing of drug prescription, and determine the molecule that works best in this particular PVD [61, 62].

Persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn is a transient form of PAH, associated with multiple antenatal and perinatal conditions, including prematurity, low birth weight, pre-eclampsia and infections. The pre- and perinatal events associated with persistent PH

of the newborn could lead to abnormal pulmonary vascular growth and function, and might increase the risk for PAH later in life [63].

Developmental lung disorders

Pulmonary hypertension associated with developmental lung disease, including bronchopulmonary dysplasia, congenital diaphragmatic hernia and congenital pulmonary vascular abnormalities is increasingly reported, probably reflecting the improved survival of extremely premature babies. In children with bronchopulmonary dysplasia, pulmonary hypertension contributes to mortality. Among survivors, pulmonary hypertension has been shown to improve or resolve with respiratory therapy, time, and possibly pulmonary vasodilators [64]. However, there is no trial formally assessing the effect of specific therapies on children with developmental lung disorder.

Conclusion

Paediatric pulmonary hypertension is a rare disease with several different causes. Management and outcome vary according to the aetiology, and so far, pulmonary vasodilators are an accepted therapy for PAH only.

Children with pulmonary hypertension should be managed in tertiary centres with a dedicated pulmonary hypertension unit in order to: (1) benefit from a standardised and exhaustive diagnostic evaluation, (2) have access to right heart catheterisation in the safest environment possible, (3) be treated according to the latest guidelines and (4) be included in clinical studies in order to continue to improve scientific knowledge on this rare disease.

Disclosure statement

JW has nothing to disclose. MB has received grants from Actelion and Bayer, contracted as consultant and participated in steering committees for Actelion, Bayer, GSK, Eli Lilly and Acceleron.

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You will find the full list of references online at <https://cardiovascmed.ch/article/doi/CVM.2023.02212>.