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TREATMENT OPTIMALIZATION IN PEDIATRIC PULMONARY HYPERTENSION

PhD thesis

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List of abbreviations

AVT – acute vasodilator testing

BNP – brain natriuretic peptide

BPD – bronchopulmonary dysplasia

CCB – calcium channel blocker

cGMP – cyclic guanosine monophosphate

CHD – congenital heart disease

CT – computed tomography

CPET – cardiopulmonary exercise test

CTEPH – chronic thromboembolic pulmonary hypertension

DLCO – diffusing capacity of the lung for carbon monoxide

ERAs – endothelin receptor antagonists

GC – guanylate cyclase

HR-QOL – health-related quality of life

iPAH/fPAH – idiopathic/familial pulmonary arterial hypertension

LV – left ventricle

LuTx – lung transplantation

mRAP – mean right atrial pressure

MRI – magnetic resonance imaging

mPAP – mean pulmonary arterial pressure

NO – nitric oxide

NT-proBNP – N-terminal fragment of prohormone of brain natriuretic peptide

PAH – pulmonary arterial hypertension

PAP – pulmonary arterial pressure

PDE5i – phosphodiesterase type 5 inhibitors

PH – pulmonary hypertension

PPHN – persistent pulmonary hypertension in the newborn

PVR – pulmonary vascular resistance

PVRi – pulmonary vascular resistance index

PWCP/PAWP – pulmonary wedge capillary pressure/pulmonary arterial wedge pressure

RA – right atrium

RV – right ventricle

6-MWT – 6-min walk test

QoL – quality of life

PA – pulmonary artery

PCH – pulmonary capillary haemangiomatosis

PEA – pulmonary endarterectomy

PVOD – pulmonary veno-occlusive disease

RHC – right heart catheterization

RV – right ventricle

SVR – systemic vascular resistance

TAPSE – tricuspid annular plane systolic excursion

V/Q – ventilation/perfusion

WHO FC – World Health Organization functional class

WSPH – World Symposium on Pulmonary Hypertension

WU – Wood Units

1. Introduction

Pulmonary hypertension (PH) is a rare disease with poor prognosis and diverse etiology in pediatric patients. With a few specific exceptions (such as PH associated with bronchopulmonary dysplasia (BPD) or congenital diaphragmatic hernia), the course is similar, with progressive damage to the pulmonary vasculature, which is irreversible in the majority of cases. However, the dynamics of the disease may vary depending on the etiology, so proper diagnosis is as important as personalised treatment. In addition to non-invasive diagnostics, invasive hemodynamic testing is of particular importance, because the hemodynamic definition is used to confirm the diagnosis of the disease. Once the diagnosis of PH is confirmed, therapeutic options can be decided.

1.1. Definition, pathomechanism and classification

Definition

After birth, the circulatory system, which operates with balanced ventricular pressures during foetal life, gradually converts to the normal hemodynamic values of childhood/adult life. The pulmonary vascular resistance (PVR), which is still variable during transitory circulation, normalises within a few weeks. Accordingly, PH is defined as a rise in mean pulmonary arterial pressure to an abnormal range (mPAP>=25 mmHg) on hemodynamic examination after 3 months of age. In the case of pulmonary arterial hypertension (PAH), the pulmonary capillary wedge pressure (PCWP) is not elevated (PCWP<=15 mmHg) and use of the pulmonary vascular resistance index (PVRi) is also recommended for the diagnosis of PAH in childhood. Pulmonary vascular disease (PVD) is confirmed if PVR >3 Wood Units (WU) (**1**).

In the recent adult guideline, the PAH criteria was changed to mPAP>=20 mmHg and PVR>2 WU having in mind that this is a progressive disease which has to be diagnosed as early as possible (**2**). How much relevance the new criteria have in children remains subject to further investigation (**3**).

Pathomechanism

Vascular remodelling in the pulmonary arterioles is the most common feature of PAH, affecting all three layers of the vascular wall (intima, media, adventitia). The triggering factor may be wall stress due to increased pulmonary flow (CHD-associated forms),

hypoxia and/or mechanical stress (PAH associated with BPD), but hereditary forms clearly indicate an important role for genetic factors (**4-6**). It has long been known that abnormalities in the mechanism of action of main vasoreactive agents play a role in the pathogenesis of PAH (NO-GC-cGMP, prostacyclin, endothelin-1 pathway) (**7**). There is an imbalance in the vascular endothelium between vasodilator (NO, prostacyclins) and vasoconstrictor agents (endothelin, thromboxane), with vasoconstriction predominance. In addition, a number of factors contribute to disease progression, including inflammatory processes, endothelial dysfunction and abnormal vascular wall proliferation (**8**). Due to the abnormal proliferation of endothelial cells, resistance to apoptosis the cancer-like characteristics of PAH has emerged (**9**). Intimal injury, smooth muscle hypertrophy, necrosis, plexiform lesions, thrombosis characterise the histological findings. The disease is progressive in the vast majority of cases, with vascular remodelling leading to a gradual increase in PVR, which after a gradual increase in pulmonary pressure, leads to right ventricular dysfunction and circulatory failure.

Classification

During childhood, PH is most often caused by persistent pulmonary hypertension in the newborn (PPHN) or congenital heart disease (CHD), but with PH being transient in most cases in both groups. In addition to the transient forms, PH associated with cardiac disease (PAH-CHD) or bronchopulmonary dysplasia in preterm infants is relatively common, while the idiopathic form (iPAH) and the form associated with hereditary or connective tissue disease and pulmonary veno-occlusive disease (PVOD) are rare (**10**). Because of the high prevalence, PAH-CHD have also been grouped according to hemodynamics and complexity (**11**). In addition, especially in adulthood, many other etiologies were described (**2**). I used the clinical classification used at the time of my studies (**Table 1**).

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Table 1. Updated clinical classification of pulmonary hypertension – 6th World Symposium on Pulmonary Hypertension (3)

Group 1. PAH 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 PVOD/PCH 1.7 Persistent PH of newborn syndrome	**Group 4. PH due to pulmonary artery obstructions** 4.1 Chronic thromboembolic PH (CTEPH) 4.2 Other pulmonary artery obstruction
Group 2. PH due to left heart disease 2.1 PH due to heart failure with preserved LVEF 2.2 PH due to heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH	**Group 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
Group 3. PH due to lung diseases and/or hypoxia 3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung diseases with mixed restrictive/obstructive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders	

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

1.2. Diagnosis and risk stratification

The diagnosis of pulmonary hypertension may be made in the context of an underlying disease (CHD, BPD, scleroderma, CTEPH). When PH is suspected during the screening (most commonly by echocardiography), a hemodynamic study should be performed to

confirm the diagnosis. If the underlying disease is unknown (idiopathic and hereditary forms, rarely unrecognised CHD), aspecific symptoms (fatigue, reduced exercise capacity, potentially syncope) may indicate the development of right ventricular failure, which may be caused by PH, most often in an advanced stage. The presence and severity of clinical symptoms are important for the diagnosis and treatment of PH. Adult functional classification based on clinical signs (World Health Organization functional class – WHO FC) has limitations in children, but other functional classification for children has not been widely adopted (**12**) (**Table 2**).

Table 2. WHO functional classification of pulmonary hypertension (12)

Class	Symptoms
I.	Patients with PH but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain or near syncope
II.	Patients with PH resulting in slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnea, fatigue, chest pain or near syncope
III.	Patients with PH resulting in marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes undue dyspnea, fatigue, chest pain or near syncope
IV.	Patients with PH resulting in inability to carry out any physical activity without symptoms. These patients have manifest symptoms of right heart failure. Dyspnoe and/or fatigue may be present even at rest. Discomfort is increased by any physical activity undertaken. Syncope or near syncope can occur

WHO: World Health Organization; PH: pulmonary hypertension

If PH is identified, the diagnostic algorithm leading to the exact etiology must be followed (**3, 13**) (**Figure 1**).

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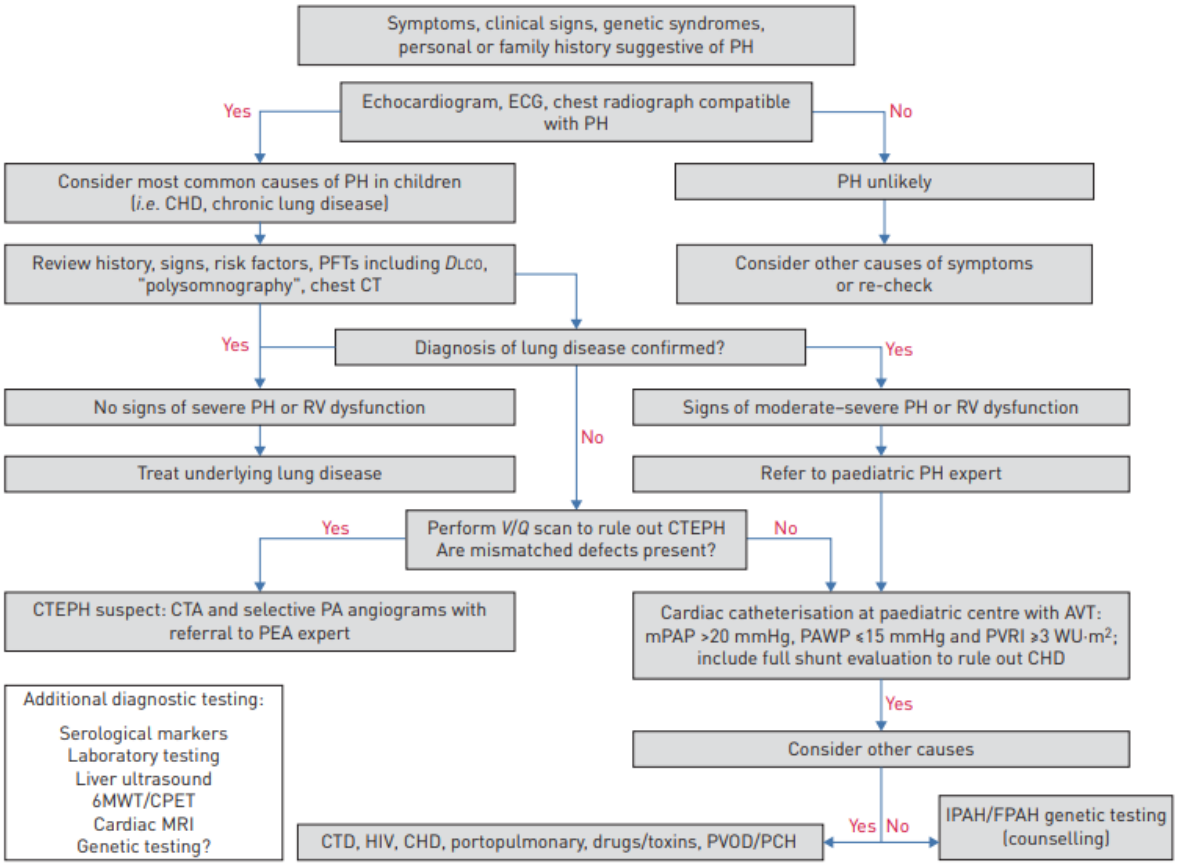


CHD: congenital heart disease; PFT: pulmonary function test; DLCO: diffusing capacity of the lung for carbon monoxide; CT: computed tomography; RV: right ventricular; V/Q: ventilation/perfusion; CTEPH: chronic thromboembolic PH; CTA: CT angiography; PA: pulmonary artery; PEA: pulmonary endarterectomy; AVT: acute vasodilator testing; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVRI: pulmonary vascular resistance index; WU: Wood Units; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise test; MRI: magnetic resonance imaging; CTD: connective tissue disease; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; IPAH/FPAH: idiopathic/familial pulmonary arterial hypertension

Figure 1. Diagnostic algorithm for pulmonary hypertension in children (3)

The etiology is of prognostic importance for the survival of patients with pulmonary hypertension and therefore influences the therapy. In addition to the etiology, several risk factors determining prognosis have been identified in recent years. The risk stratification proposed by the international guideline, which has been introduced mainly for the

idiopathic form, defines high and low values of the risk factors in childhood and examines the presence of a given risk factor, which then forms the basis for the choice of therapy.

In 2013, for the first time the 5th WSPH Paediatric Task Force (World Symposium on Pulmonary Hypertension) identified the most important factors that put children at higher risk of poor outcome (**14**) (**Table 3**). Subsequent analysis of determinants confirmed the importance of NT-proBNP, WHO FC and echocardiographic parameters such as tricuspid annular plane systolic excursion (TAPSE), which were correlated with survival during follow-up (**15**).

Table 3 Pediatric determinants of risk (2013) (14)

Lower risk	Determinants of risk	Higher risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I-II	WHO FC	III-IV
Minimally elevated	Serum BNP/NT-proBNP	Significantly elevated Rising level
	Echocardiography	Severe RA/RV enlargement Pericardial effusion
Systemic CI>3.0 l/min/m2 mPAP/mSAP<0.75 Acute vasoreactivity	Hemodynamics	Systemic CI<2.5 l/min/m2 mPAP/mSAP>0.75 mRAP> 10 mmHg PVRi>20 WU*m2

RV: right ventricle; WHO: World Health Organization; FC: Functional Class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; CI: cardiac index; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; mSAP: mean systolic arterial pressure; PVRI: pulmonary vascular resistance index; WU: Wood Units

In 2018, the 6th WSPH Paediatric Task Force partially modified the risk stratification, removing syncope from the list, while including TAPSE among the echo parameters (**3**) (**Table 4**).

Currently, risk factors in children include the presence or absence of right ventricular failure, symptom progression, 6-minute walk test (6-MWT), WHO FC, level of BNP/NT-proBNP, echocardiographic and hemodynamic parameters. Patients are considered at high risk if they have symptoms of right ventricular failure, progressing symptoms, significantly elevated BNP/NT-proBNP level, WHO FC III-IV, and/or if they have inadequate weight gain. Poor prognosis is indicated by right ventricular (RV) dysfunction seen on echocardiography, reduced left ventricular (LV) diameter, increasing right/left ventricular index, reduced TAPSE, and pericardial effusion. Among the hemodynamic parameters, decreased cardiac index, increased mean right atrial pressure (mRAP), significantly elevated PVRi are the most important parameters indicating poor outcome (CI<2.5 l/min/m2, PVRi>20 WU*m2, mRAP>10 mm Hg) (**Table 4.**).

Table 4. Determinants of pediatric idiopathic/heritable PH risk (2018) (3)

Lower risk	Determinants of risk	Higher risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
>350	6 MWT (>6 years old) m	<350
Normal	Growth	Failure to thrive
I-II	WHO FC	III-IV
Minimally elevated	Serum BNP/NT-proBNP	Significantly elevated Rising level
	Echocardiography	RA/RV enlargement Reduced LV size Increased RV/LV ratio Reduced TAPSE LOW RV FAC Pericardial effusion
Systemic CI>3.0 l/min/m2 Systemic venous saturation>65% Acute vasoreactivity	Haemodynamics	Systemic CI<2.5 l/min/m2 mRAP> 10 mmHg PVRi>20 WU*m2 Systemic venous saturation<60% PACI<0.85 ml/mmHg/m2

RV: right ventricle; 6MWT: 6-min walk test; WHO: World Health Organization; FC: Functional Class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; LV: left ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; CI: cardiac index; mRAP:

mean right atrial pressure; PVRI: pulmonary vascular resistance index; WU: Wood Units; PACI: pulmonary arterial compliance index.

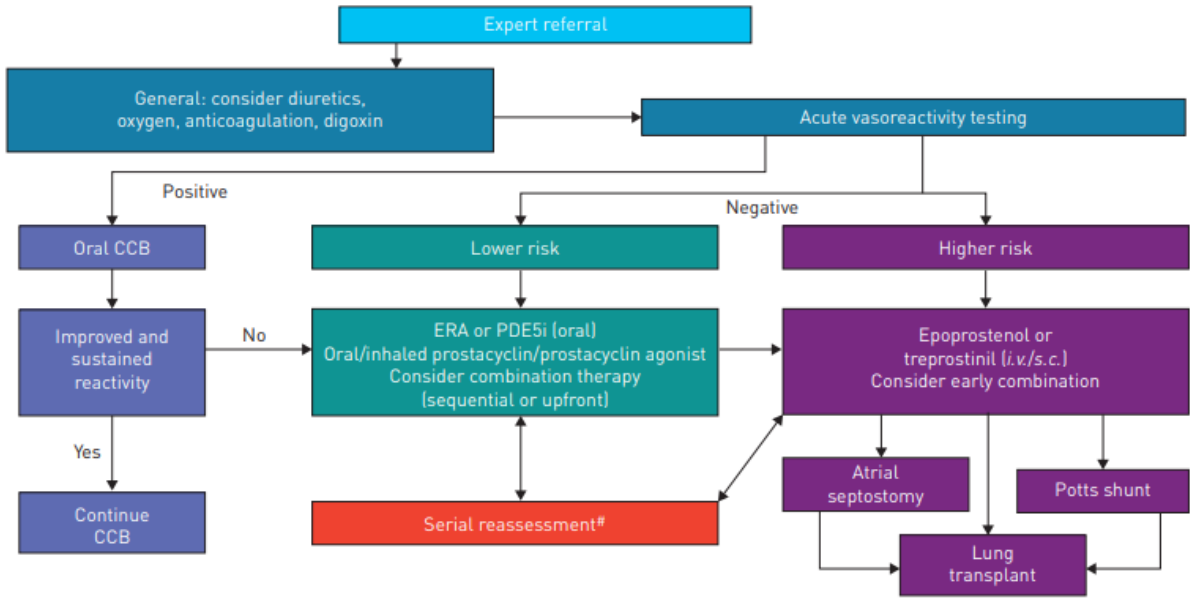
Looking ahead, it is worth taking into account the latest adult guideline (2022) which suggests a differentiation in the risk criteria depending on the timing of use, when the diagnosis is made, or clinical deterioration is observed. All invasive and noninvasive parameters should be taken into account (3 strata model), vs. regular follow-up which uses only WHO FC, NT-proBNP/BNP and 6-MWD (4 strata model) (**2**). Whether this will be applicable to the pediatric population has to be confirmed in further studies.

1.3.Treatment options

Despite the diverse etiology in childhood, therapeutic guidelines are similar, especially in advanced (high-risk) stages. The hemodynamic work-up, which confirms the diagnosis and has a major impact on therapy, involves an acute vasoreactivity test, most commonly with inhalation of 20-40 ppm nitric oxide (NO). We consider pulmonary hypertension to be vasoreactive if pulmonary pressure decreases significantly (Barst criterion: mPAP decrease > 20%, unchanged or increasing CI, or decreasing or unchanged PVR/SVR ratio) during the drug test (**16**). Vasoreactivity in itself suggesting a good prognosis (**17**), rarely seen in our practice. In vasoreactive cases, calcium channel blocker (CCB) is indicated, which also causes vasodilation in pulmonary arteries. However, in the vast majority of patients, in the absence of vasoreactivity, PAH-specific therapy is initiated, either monotherapy or combination therapy, according to the risk stratification (**3**) (**Figure 2**).

For children, the therapeutic algorithm applies to patients with iPAH, with no clear recommendation for other forms of PH. Adult guideline suggests that the same treatment strategies should be used for PAH associated with CHD as for iPAH, with the exception of Eisenmenger syndrome, where monotherapy is the first choice and a switch to combination therapy is recommended if there is no improvement (**2**).

The main PAH-specific drugs used in children are endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5i) and prostacyclin analogues.



CCB: calcium channel blocker; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitors

Figure 2 Pediatric iPAH treatment algorithm (3)

Endothelin receptor antagonists (ERAs)

Endothelin is a potent vasoconstrictor agent produced in vascular endothelium and smooth muscle. Its action is mediated through endothelin receptors (type A and B). ERAs have been shown in clinical trials to improve hemodynamics, functional status and survival (**18**). A trial of bosentan in pediatric patient population has proven clinical utility and has been licensed in Europe (**19**). Our experience shows that it is a well tolerated PAH specific agent in children, with side effects being such as effect on liver function and teratogenicity. Clinical trials in children are ongoing for ambrisentan and macitentan (**20**).

PDE5 inhibitors

PDE5 inhibitors inhibit the degradation of cGMP, resulting in pulmonary vasodilation. They are also known to have anti-proliferative and ventricular function improving functions, both beneficial in PH. Side effect profile is relatively favourable in all age groups (**21**). They have a significant role in weaning neonates/infants receiving

postoperative NO treatment for PH off ventilators and therefore pediatric cardiac surgery departments have considerable experience in their usage. Sildenafil is the first of this group to be widely used in pediatric cardiology as the agent of choice in PH associated with BPD in preterm infants. There is also growing experience with long half-life tadalafil in children, with once-daily dosing being particularly beneficial in the pediatric population.

The guanylate cyclase stimulator riociguat, like PDE5 inhibitors, acts via the NO pathway and it has been shown to be effective in the treatment of PAH in adult studies. Pediatric studies are ongoing, pending the outcome of which a wider use in the pediatric population is expected (**22**).

Prostacyclin analogues

Prostacyclin is an endogenous vasodilator agent produced in the vascular endothelium that acts on both systemic and pulmonary circulation. It also has anti-proliferative, anti-inflammatory and anti-thrombotic effects. Epoprostenol treatment was the only available PAH-specific therapy in children before the 2000s. Its widespread use as a first-line therapy was hampered by the need for central venous cannulation due its rapid half-life (3-5 minutes), the associated risk of infection and thrombosis, and the difficulties associated with age (**23**). With the availability of oral PAH-specific therapies, intravenous prostacyclin therapy has become a second-line treatment. However, despite new treatment options, the prognosis of PAH remains poor, especially in the idiopathic/hereditary group. At the same time, subcutaneous treprostinil treatment became available in children as a functional alternative to intravenous administration (**24**). The current pediatric therapeutic guide-line recommends parenteral prostacyclin for high-risk cases subcutaneously or intravenously as monotherapy or as part of a combination regiment (**25**). The oral prostacyclin receptor agonist selexipag is also a new therapeutic option in children, but its use is off-label due to ongoing clinical trials (**26**). Inhaled prostacyclin is rarely used in children, mainly because of its bronchoconstrictor effect (**27**).

Combination therapies

In line with the risk stratification in children, and taking into account the very poor prognosis of PAH, combination therapy is recommended even in the low-risk group, mainly with a combination of oral agents (PDE5i and ERA), either up-front or as sequential treatments. In advanced cases (high-risk group), parenteral prostacyclin therapy, subcutaneous or intravenous, should be part of the treatment (**2**, **28**). It is important to consider combination therapy if there is no change to low-risk status with prostacyclin therapy, as this should ultimately be the main goal of treatment. The treatment used should always take into account the age of the child, parent-child compliance, etiology and the possibility of other (surgical) therapies. Our studies also aimed to define guidelines for optimal therapy tailored to individual children.

Other treatment options

The novel use of Potts shunt (a non-restrictive connection between the descending aorta and the left pulmonary artery), proposed in recent years by a French working group and successfully applied in several centres, has become an alternative solution for severe PAH resistant to drug therapy. The Potts shunt is indicated in cases of suprasystemic pulmonary arterial pressure. Due to non-restrictive connection the pulmonary pressure is reduced to systemic levels at the cost of significant right-to-left shunt-induced lower body cyanosis, resulting in a significant reduction in right ventricular afterload (**29**). Eisenmenger-like hemodynamics improves prognosis, while at the same time the brain and coronary arteries receive O2-rich blood, a significant advantage over Eisenmenger patients. The Potts shunt is preferred to the atrial septectomy, which only indirectly reduces right ventricular pressure (via pulmonary flow reduction) (**30, 31**). The beneficial effect of the Potts shunt is maintained in the longer term after postoperative period (although perioperative complications are not negligible), even when parenteral therapy is converted to oral therapy. After Potts shunt, if the disease progresses or symptoms do not improve, there is still the option of lung transplantation (LuTx).

Lung transplantation is the only option for end-stage PAH that can significantly prolong life in patients treated with maximal drug therapy, in addition to a Potts shunt. After LuTx, patients requiring lifelong immunosuppressive therapy are at risk of acute and chronic rejection, and may develop secondary diseases. LuTx is indicated if the patient receiving

maximal therapy (triple PAH specific therapy including parenteral prostacyclin), is not suitable for Potts shunt and life expectancy is less than 2 years with poor quality of life without the organ transplantation. In patients treated with maximal drug therapy, the development of acute right heart failure has a very poor short-term outcome. Depending on the age, donor-recipient size mismatch can significantly increase waiting time in children and thus waiting list mortality. In rapidly progressive cases, the need for pre-transplant ECMO support should be considered, which represents an extra additive risk (**32**). The expected waiting time on the waiting list varies between lung transplant centres, partly depending on which international donor organisation the centre belongs to. Due to the long-term effectiveness of lung transplantation, it is primarily considered in the adolescent age group, at end-stage (**33**).

In our practice, if the patient on triple PAH specific therapy including parenteral prostacyclin, has markedly reduced functional capacity (WHO FC III-IV), NT-proBNP level is increasing and the child is suitable for LuTx given his/her age and underlying disease, referral to the lung transplant committee is recommended. Due to their age and rapid progression, children are assigned HU (high urgency) status on the waiting list in the Eurotransplant system.

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2. Objectives

In Hungary, the Pediatric Heart Center of Gottsegen National Cardiovascular Center is dedicated for pediatric cardiology and pediatric cardiac surgery. Every year we perform 450-500 cardiac surgeries, about 250 cardiac catheter interventions and about 120 catheter ablations. We are also a pediatric heart transplant and PAH centre. Our centre started specialised treatment of PAH patients 20 years ago and since then we have treated nearly 160 children. We currently treat 50-60 patients for PAH every year. After a systematic review of risk assessment, treatment outcomes and quality of life, we set the following goals:

2.1.To determine the prognostic value of early risk stratification in pediatric PAH

- 2.1.1. Impact of etiology on prognosis
- 2.1.2. Significance of different risk factors, the number of risk factors
- 2.1.3. Evaluation of hemodynamic risk factors for transplant-free survival

2.2. Analysis of our pediatric experience of subcutaneous treprostinil treatment as part of advanced PAH treatment

- 2.2.1. Assessment of tolerability of subcutaneous treprostinil therapy in children
- 2.2.2. Study of disease progression in children treated with subcutaneous treprostinil
- 2.2.3. Dose-titration and target dose achievement rate

2.3. To assess QoL in our PAH patient population

- 2.3.1 Comparison of iPAH and CHD in terms of QoL
- 2.3.2 Investigation of the association between age and QoL
- 2.3.3 Examination of PAH risk factors in terms of QoL

All of the following studies were performed in accordance with the Declaration of Helsinki

(ethical permissions: SE RKEB numbers 125/2020, 127/2020)

3. Methods

3.1. Risk stratification study

The database of 58 pediatric PAH patients treated between 1995 and 2019 at our centre was reviewed retrospectively. PAH patients were classified according to Rosenzweig et al (**3**) (**Table 1**). Out of 58 pulmonary hypertensive patients, 12 patients had idiopathic pulmonary hypertension (group 1.1), 32 patients had PAH associated with congenital heart disease (CHD) (group 1.4.4), 2 patients had connective tissue disease (group 1.4.1), 2 patients had PAH associated with lung disease (group 3), and 10 patients had multifactorial PAH with complex heart disease (group 5). Due to the lack of initial hemodynamic measurements, PAH patients associated with BPD were excluded. Basic patient characteristics are shown in **Table 5**.

Table 5. Patient characteristics

Sex (male)	29 (50%)
Age at diagnosis (years)	4.2 (0.1-16.1)
Weight at diagnosis (kg)	15.5 (3.4-95.4)
Height at diagnosis (cm)	103 (56-168)
Follow up time (years)	5.4 (0.0-24.1)

continuous variables presented as median (minimum-maximum)

Baseline data collected at the time of diagnosis were demographics, WHO FC, echocardiographic and hemodynamic parameters. Echocardiographic parameters considered as signs of possible PAH were RA/RV enlargement, reduced LV size, increased RV/LV ratio, reduced TAPSE, and pericardial effusion. Hemodynamic parameters included mRAP, mPAP, PWCP, and mean arterial pressure. Systemic and pulmonary blood flows, indexed resistances (systemic and pulmonary vascular resistance index - WU*m2) were calculated. Determinants of elevated PAH risk (**3**) were cardiac index < 2.5 L/min/m2 , mRAP> 10 mmHg, PVRI > 20 WU*m2 , and systemic venous saturation < 60%. NT-ProBNP level testing was not performed routinely at the time of diagnosis. As the median age of our patients was only 4.2 years, the 6-MWT was not performed routinely

Statistical analysis

Categorical variables are presented as counts (percentages), and continuous variables are given as median (minimum-maximum). Univariate survival curves were estimated with the nonparametric method of Kaplan-Meier. Multivariate modelling of the survival times was performed with Cox proportional hazards model; results are presented as hazard ratios with 95% confidence intervals. Continuous variables were first expanded with restricted cubic splines (to allow for potentially nonlinear effects), and were only used in linear form if the deviation from linearity was nonsignificant with global F test [6]. Effects were considered significant if $P < 0.05$. Statistical analysis was performed under R program (R Foundation for Statistical Computing, Vienna, Austria) package version 3.6.2 using package rms, version 5.14.

3.2. Subcutaneous treprostinil study

The database of 56 pediatric PAH patients treated between 2006 and 2016 in our institute was reviewed retrospectively. From our 56 PAH patients, 32 patients had PAH associated with CHD (group 1.4.4), 9 patients had PH associated with lung disease (7 pts with BPD) (group 3), 3 patients had connective tissue disease (group 1.4.1), and 12 patients had iPAH (group 1.1). Exclusion of other causes of PH were conducted according to the guidelines.

During the study period, 8 patients were treated with subcutaneous treprostinil. 7 of 8 patients had iPAH (group 1.1) and 1 had PAH associated with pulmonary hypoplasia and complex congenital malformations (group 3).

Basic patient characteristics are listed in **Table 6**.

Table 6. Patient characteristics

Pt	Dg	Age at diagnosis (years)	PVRi at dg (WU*m2)	TR at dg (m/s)	Age at TREin (years)	WHO func st at TREin	NT-proBNP at TREin (pg/ml)
1	iPAH	8.1	8.6	5.0	13.4	III	8042
2	iPAH	13.6	21.2	4.6	14.7	III	3950
3	aPAH	2.4	10.5	4.8	8.4	IV	6900
4	iPAH	10.3	13.8	4.2	11.4	III	2294
5	iPAH	1.4	5.2	4.7	2.6	III	8656
6	iPAH	12.5	17.1	5.4	14.2	IV	not performed
7	iPAH	3.1	15.6	4.6	4.2	IV	19653
8	iPAH	1.9	16.5	5.0	14.3	III	not performed

Pt: Patient; Dg: Diagnosis; TRE: treprostinil; TREin: treprostinil initiation; WHO func st: WHO functional status; PVRi: pulmonary vascular resistance index; WU: Wood Units; TR: tricuspid regurgitation; NT-proBNP: N-terminal fragment of the prohormone of brain natriuretic peptide

Their median age at PAH diagnosis was 5.6 years (range 0.6-12.5); median age at treprostinil initiation was 12.4 years (range 2.6-14.7). All patients were on PDE5i (sildenafil) and/or ERA (bosentan or ambisentan) therapy before treprostinil initiation. The median age at escalation to dual therapy was 11 months (1-66 months) and then to triple combination therapy 8.5 months (3-22 months). 2 patients had previously been on parenteral prostacyclin (iloprost) for 13 and 43 days.

Baseline data collected at the time of diagnosis and before the initiation of treprostinil were as follows: demographics, WHO FC, serum NT-proBNP levels, echocardiographic parameters and hemodynamic data. Calculated parameters were systemic and pulmonary blood flow and indexed resistances (SVR and PVR in WU*m2). Patients were reexamined at 3 to 6 month intervals and collected data included WHO FC and echocardiogram. NT-proBNP was measured only at time of clinical worsening.

Indications for initiation of subcutaneous treprostinil therapy were clinical worsening of symptoms (WHO FC III-IV) and/or echocardiographic progression (decreased cardiac output) or switch from intravenous to subcutaneous therapy.

The initial treprostinil dose was 2 ng/kg/min, increasing to 10 ng/kg/min over 5 days. Subsequent dose adjustments were made based on clinical symptoms (during routine controls every 4-12 weeks). Slow up-titration was carried out during the switch from intravenous to subcutaneous treprostinil therapy. Target dose was defined as 60 ng/kg/min. Treprostinil was administered as a continuous subcutaneous infusion via an ambulatory microinfusion pump.

Specially trained nurse was responsible for educating both parents and patients on side effect monitoring.

3.3.QoL study

Data of 25 patients (aged 2–18 years, 17 male) with a diagnosis of PAH requiring medical treatment was reviewed in this cross-sectional study. Of 25 PAH patients according to clinical classification (**Table 1**) 1 had idiopathic pulmonary hypertension (group 1.1), 15 patients had PAH associated with CHD (group 1.4.4), 2 patients had PAH associated with lung disease (group 3), 7 patients had multifactorial PAH with complex heart disease (group 5). Basic patient characteristics are shown in **Table 7**.

Table 7. Basic patients' characteristics

Sex (male)	17 (68%)
Age at diagnosis (years)	4.0 (4.5)
Age (years)	9.5 (4.9)
Weight (kg)	33.4 (25.4)
Weight (Z score)	-1.1 (1.5)
Height (cm)	130.0 (25.9)
Height (Z score)	-0.7 (1.2)
BMI (kg/m2)	17.8 (8.1)
BMI (Z score)	-0.8 (1.8)

continuous variables are presented in mean +- standard deviation

To assess the PAH patients' health-related quality of life (HR-QL), the validated Hungarian version of the Pediatric Quality of Life Inventory (PedsQL^{TM}) 4.0 Generic Core Scales (QL-GCS) and the PedsQL^{TM} 3.0 Cardiac Module (QL-CM) were used. The reference data of the QL-CM summarises the results of the entire cardiological spectrum and it also contains a more detailed breakdown depending on the severity of heart disease, including simple CHD (such as isolated small or repaired ventricular septal defect without residua), CHD with moderate complexity (for example coarctation of the aortae, moderate-to-severe pulmonary valvar disease or tetralogy of Fallot) and the most severe CHD with grand complexity (such as univentricular heart or condition with conduits or Fontan patients).

The QL-GCS has 4 (physical, emotional, social, school functioning), whereas the QL-CM has 6 (heart problems-symptoms, treatment, perceived physical appearance, treatment anxiety, cognitive problems, communication) domains with child self-report and parent proxy-report formats. Child self-report and parent proxy-report includes ages 5-7 years (young child), 8-12 years (child), and 13-18 years (adolescent), the parent survey includes an extra 2-4 years (toddler) format. Patients aged 5–18 years with appropriate mental/cognitive capacity completed both age specific QL-GCS and QL-CM.

The parent report and the self-report questionnaire used a 5-point Likert score (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = always). It was linearly transformed, resulting in a score of 0–100; higher scores indicating better pediatric quality of life.

In addition, we have calculated Psychosocial Health Summary Score (Psychosocial Sum), where the sum of the Likert scores is divided by the number of questions answered in the Emotional, Social, and School Functioning Modules.

At the time of the study, WHO FC, symptoms of right heart failure, echocardiographic parameters (TAPSE - mm/Z score, left ventricular end-systolic diameter - mm/Z score, left ventricular end-systolic eccentricity index) were available as risk stratification data. NT-proBNP levels were also available in 50% of patients. Hemodynamic measurements were performed within one year in 20% of children. Regarding specific therapy for PAH, 18 patients were on monotherapy, 6 patients were on dual oral therapy and only 1 patient was receiving triple therapy including prostacyclin at the time of the study.

Statistical analysis

Categorical variables are presented as counts (percentages), continuous variables are given as mean ± standard deviation (SD) or median (range) where applicable. In subgroup analysis we have used Wilcoxon rank sum test and ANOVA where appropriate. Effects are considered significant if $p<0.05$. The SPSS statistical package version 27.0 (IBM, Armonk, New York) was used to perform all statistical evaluations.

4. Results

4.1. Risk stratification study

The majority of patients were in a stable clinical status at diagnosis (WHO FC I-II 56/58 cases). Clinical signs of right heart failure were more frequent (25/58), mainly in the form of fatigue and exertion complaints. This difference between stable clinical status and the presence of symptoms of right heart failure also shows the difficulty of accurately assessing WHO FC in children. Growth failure was observed in ¼ of children. The presence of at least 1 of the echocardiographic parameters suggestive of poor prognosis was confirmed in more than half of the patients (35/57, 61.4%). Hemodynamic parameters at time of diagnosis are shown in **Table 8**. At least 1 of the hemodynamic parameters reached a value which could be classified as high risk (CI<2.5 l/min/m2, mRAP>10 mm Hg, PVRi>20 WU*m2, SVO2<60%) in nearly half of the patients (48%).

Table 8. Hemodynamic parameters at the time of diagnosis

Hemodynamic parameters	Value
Cardiac index (l/min/m2)	3.5 (1.3-7.4)
Mean right atrial pressure (mRAP) (mmHg)	9 (3-29)
Systemic venous saturation (%)	68 (30-82)
Pulmonary vascular resistance index (PVRI) (WU*m2)	10.4 (3.7-70.0)

variables are given in median (range)

The average follow-up was 5.4 years, with a mortality rate of 29%. Altogether 33% of patients reached the composite endpoint (death or lung transplant).

In terms of poor outcome, idiopathic and CHD-associated forms were compared, the latter predicting a significantly better prognosis (even after adjusting for age (hazard ratio = 0.12 [95% confidence interval: 0.03-0.48], P = 0.0024) (**Figure 3/a, 3/b**). Probably due to the low number of cases, neither WHO FC (P = 0.0866), nor clinical signs of right ventricular failure (P = 0.2760) or developmental delay (P = 0.630) had significant prognostic value in our study.

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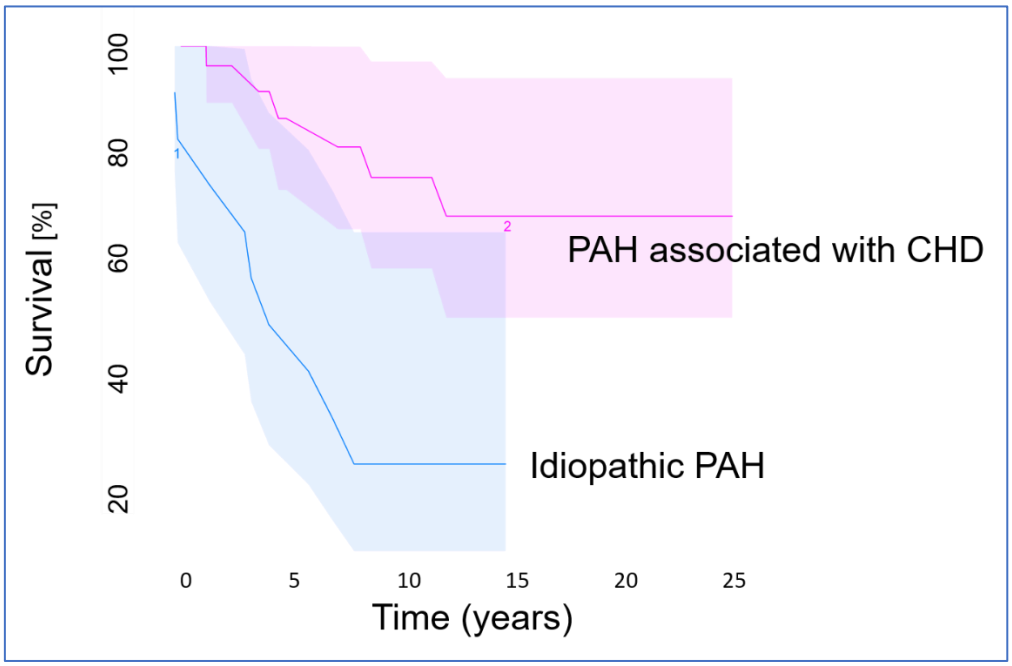

Figure 3/a. Mortality in iPAH (n=12) compared to the patients with CHD associated PAH (n=32)

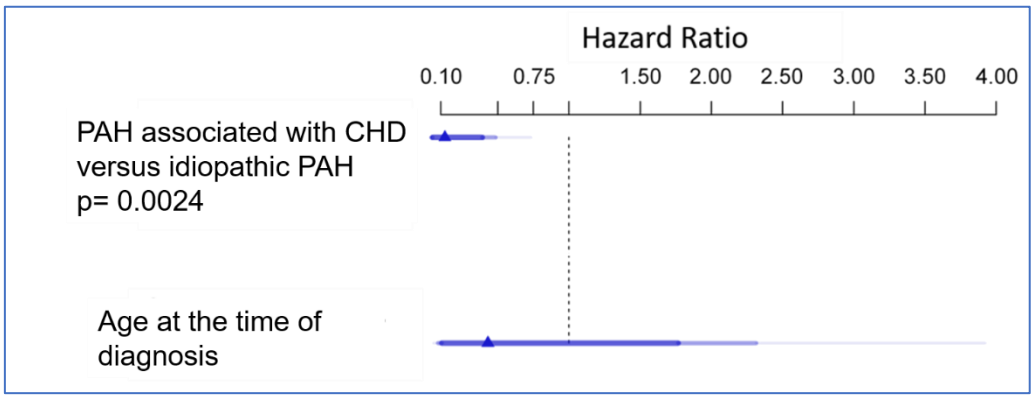

Figure 3/b Multivariate analysis of mortality in patients with CHD associated PAH (n=32) compared to the patients with iPAH (n=12)

Similarly, the echocardiographic parameters were not found to be prognostic determinants (P = 0.0576).

Due to their importance, hemodynamic parameters were analysed separately. First, taking into account the pathological cut-off values defined by the risk stratification, we compared the group of patients with one or more pathological values to children with

hemodynamic parameters in the normal range and there were no significant difference between the two groups. Considering PVRi alone as the most important parameter, we found a 49.1% higher hazard ratio for every 10 WU*m2 increase in PVRi (95% confidence interval: 1.13-1.97, P = 0.0048) (**Figure 4**)

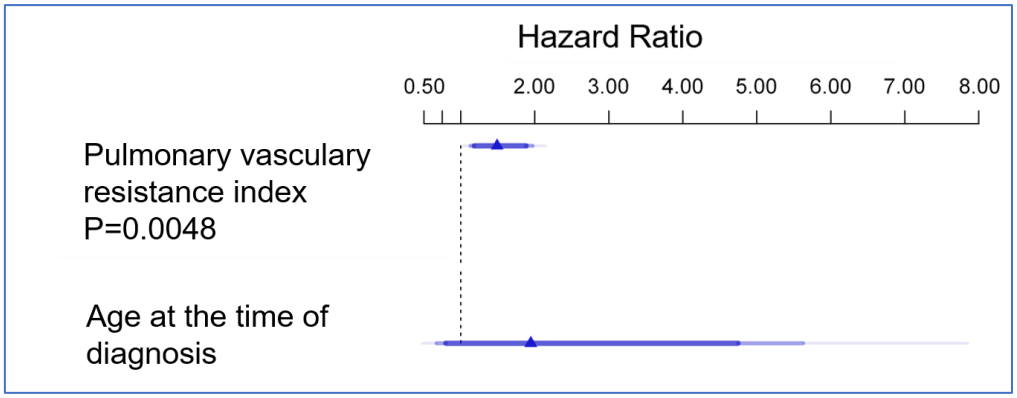

Figure 4. Effect of PVRi on mortality in our pediatric PAH population - multivariate analysis

We also analysed the number of risk factors at the time of diagnosis. We found an average of 2 risk factors, with an average of 2.5 in iPAH patients and an average of 1 in CHD-related PAH. The number of risk factors alone was not associated with worse prognosis in the study population (P=0.1534).

4.2. Treprostinil study

After the above described initiation and titration of subcutaneous treprostinil, patients had their dosage increased to the target level of 60 ng/kg/min treprostinil (median (range 10-100) ng/kg/min). Two patients died early after treprostinil initiation (one after 3 days and the other after 7 days) due to PAH progression (**Table 9**).

Table 9. Treprostinil therapy characteristics and outcome

Pt	Dg	Time on TRE (years)	Final TRE dose ng/kg/min	WHO FC change	Outcome
1	iPAH	1.57	70	=	death on lung tx waiting list
2	iPAH	2.31	60	=	lung tx, survival
3	aPAH	4.31	60	↓	survival
4	iPAH	2.10	100	↑	Potts shunt, lung tx, survival
5	iPAH	0.33	80	=	Potts shunt, death
6	iPAH	0.003	10	=*	death
7	iPAH	0.02	40	=*	death
8	iPAH	0.02	10	=**	lung tx, death

iPAH: idiopathic pulmonary arterial hypertension; aPAH: associated pulmonary arterial hypertension; Pt: patient; Dg: diagnosis; TRE: treprostinil; WHO FC: World Health Organization functional class; tx: transplantation; = no change; =* no change, early death; =** no change, early lung transplant;↑ increase in WHO FC; ↓decrease in WHO FC

Maximal dose of subcutaneous treprostinil reached 100 ng/kg/min in one patient. The preferred s.c. site was the abdominal wall, even in small children. Subcutaneous set replacement was performed on average 2-3 times per month**.** The most common adverse events were pain and local reactions at the s.c. site, which were managed by s.c. site change and minor analgesics (paracetamol). Every patient required oral or local paracetamol each time after the injection site was changed for 3-6 days. Besides paracetamol our patients did not require any other analgesic treatment. None of the patients discontinued s.c. treprostinil treatment due to site pain. Potentially due to the small patient number, no correlation was found between the local pain and treprostinil s.c. dose or volume.

Thrombocytopenia was observed on one occasion, at a high treprostinil level (100 ng/kg/min). Thrombocytopenia resolved after decreasing the treprostinil dose. No severe hypotension, nausea, headache, cough or diarrhea were reported.

Seven out of 8 patients reached end stage disease 1.0 year (median, range 0.03-2.4 years) after treprostinil initiation.

If the patients' status did not improve or stabilise after receiving the triple combination therapy (PDE5i, ERA and treprostinil), they were considered as in the end-stage of the disease and were referred to the transplant centre. The indications for lung transplantation were PAH symptoms (dyspnea, fatigue, cyanosis) after treprostinil target dose (60-70 ng/kg/min) and/or advanced WHO FC (III-IV), longstanding elevated NT-proBNP and/or decreased cardiac output.

Four patients suitable for LuTx were put on the waiting list. Three patients had a successful lung transplantation (one after Potts shunt), one died while on the waiting list.

Potts shunt as a palliative surgical technique was performed in two cases. In one patient, who was too young for LuTx, Potts shunt implantation was performed after the ineffective triple combination drug therapy, but without long-term success. In a second patient, Potts shunt was a short (54 days) bridge to successful lung transplantation. Both of these patients were transiently switched to intravenous treprostinil perioperatively. No Potts shunt function was found to be restrictive (too small) at postoperative echocardiography.

In 4 patients, lung transplantation could not be performed (age less than 3 years, overweight, severe scoliosis), 3 of whom died due to PAH progression.

The patient with scoliosis and pulmonary hypoplasia-associated PAH is still on subcutaneous treprostinil therapy. After 4.3 years of follow-up, her WHO functional class III has not changed significantly and her NTproBNP level has stabilised between 600-900 pg/ml.

4.3. QoL study

Questionnaires for different age groups were completed by children in the following age distribution: 7 patients in the 2-4 age group, 4 in the 5-7 age group, 8 in the 8-12 age group and 6 in the 13-18 age group. A total of 3 children were unable to complete the questionnaire due to mental health problems. PedsQL-GM and QL-CM Likert scores according to age are shown in **Table 10**

Table 10. PedsQL™ Generic Core Scales (PesQL™-GM) and PedsQL™ 3.0 Cardiac Module scores (PedsQL-CM) in our patients

	PedsQL™-GM		PedsQL™-CM	
	self-report	parent proxy-report	self-report	parent proxy-report
Patients aged 2-4 years (n=7)	-	92.3 (52.1-100.0)	-	78.3 (59.1-96.4)
Patients aged 5-7 years (n=4)	72.0 (70.0-100.0)	84.1 (79.6-90.5) (n=3)	82.8 (66.3-100.0) (n=3)	90.5 (75.7-100.0) (n=3)
Patients aged 8-13 years (n=8)	52.7 (41.6-91.4)	57.1 (5.0-89.8)	68.3 (28.8-91.3)	59.3 (34.8-94.3)
Patients aged 13-18 years (n=6)	66.3 (50.2-74.1) (n=3)	63.5 (48.8-71.9) (n=5)	69.0 (46.2-79.3) (n=4)	52.2 (45.4-70.2)

data expressed in median (range) value

Using PedsQL^{TM}-GM and CM data from previous studies based on Hungarian general pediatric population and that of children attending a cardiac unit with different type of heart diseases as reference (**34**, **35**), a compelling difference was found, as PAH patients have significantly lower values than the general Hungarian pediatric population in every core domain. Further, PAH patients have lower QL-CM scores than patients with different heart diseases in Physical, Emotional, Social, Psychosocial Sum domains and in total scores.

Using the detailed break-down of patients with different disease severity, PAH patient's PedsQL-CM scores were similar to those with chronic heart disease with great complexity (**35**) (**Table 11**).

Table 11. PedsQL™ Generic Core self report scores (PedsQL™-GM) of general Hungarian pediatric population, children with heart disease (CHD), CHD patients with great complexity and pediatric patients with PAH

	Healthy (n=366)		CHD (n=164)		CHD-with great complexity (n=22)		PAH (n=25)		p values	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	healthy - PAH	CHD - PAH
Physical	83.1	14.2	78.3	18.8	67.8	21.8	63.9	28.6	<0.001	0.003
Emotional	72.1	17.8	71.7	17.1	65.5	20.5	62.9	21.9	<0.001	<0.001
Social	83.8	16.1	82.6	17.5	73.3	17.7	61.8	31.1	<0.001	<0.001
School functioning	75.8	16.7	73.9	16.8	70.9	22.6	64.3	25.8	0.034	NS
Total	79.3	12.3	76.9	14.6	70.5	16.8	62.9	24.5	<0.001	<0.001
Psychosocial Sum	77.3	13.4	76.1	14.5	72.12	17.7	63.9	23.9	0.002	0.006

There was significant negative correlation between patient age and QL-CM parent proxy Likert scores ($r=-0.49$, $p<0.05$) and QL-CM parent proxy Likert scores ($r=-0.58$, $p<0.05$). There was significant positive correlation between TAPSE Z scores and QL-GCS patient self-report Likert scores ($r=0.46$, $p<0.05$) and parent proxy Likert scores ($r=0.47$, $p<0.05$). In contrast, we found no significant differences in the self-report and parent-proxy Likert scores based on Z-score values of LVIDs and similarly no significant difference was noted based on the left ventricular end-systolic eccentricity index (**Table 12**).

Table 12. Echocardiographic parameters

Echocardiographic parameters	Mean (SD)
Tricuspid annular plane systolic excursion (TAPSE) (mm)	15.4 (3.6)
Tricuspid annular plane systolic excursion (TAPSE) (Z score)	-3.3 (2.6)
Left ventricular internal diameter end-systole (LVIDs) (mm)	21.9 (5.2)
Left ventricular internal diameter end-systole (LVIDs) (Z score)	-1.1 (1.5)
Left ventricular end-systolic eccentricity index	1.5 (0.5)

There was a significant difference in parent proxy Likert scores between patients with WHO FC I and class II-IV. In addition, patients with WHO FC I had higher QL-GCS parent proxy Likert scores in School Functioning module (p=0.029) and QL-CM parent proxy Likert scores in Heart Problems and Symptoms module (p=0.014).

When comparing patients with PAH on monotherapy versus combination therapy, no significant difference could be observed in the self-report and parent proxy Likert scores.

5. Discussion

Risk stratification provides the guideline for optimal management of pediatric PAH. The clinical value of early risk stratification is difficult to determine due to the small number of pediatric patients and the diverse etiology. Despite these limitations, we have demonstrated the importance of hemodynamic testing, quality of life and tolerability of subcutaneous therapy in the choice of therapy in children.

Risk stratification

In line with our objective, we compared the iPAH and CHD-associated groups, finding that the former had a worse prognosis, even after adjusting for age. This is an important finding, as risk stratification in childhood has been tested in idiopathic and inherited forms (**36**). Accordingly, there are no accepted therapeutic guidelines for the treatment of children with PAH of different etiologies. The different prognosis depending on the etiology may be due to variable adaptation of the right ventricle. While adaptive remodelling observed in Eisenmenger's syndrome is characterised by concentric ventricular remodelling (higher mass-to-volume ratio) and preserved systolic and diastolic function, maladaptive remodelling has been observed in idiopathic PAH, which is characterised by more eccentric right ventricular hypertrophy and worse systolic and diastolic function (**37**).

One of the most important of the non-invasive risk factors is functional status. However, the assessment of functional status in young children is more difficult than in adolescents or adults. The Ross or the Panama functional classification (**12**), which is specific to children, has not been adopted in routine practice. In our study, using the WHO functional classification, advanced functional status (WHO FC III-IV) was not found to be a predictor of poor survival. This is partly due to the low number of patients, andin part because the study included predominantly children with good functional status and because it is difficult to accurately define WHO FC before adolescence. It is important to note that in our study, risk factors, including WHO FC, were assessed at the time of diagnosis, i.e. risk stratification at a later stage could have yielded different results. A previous study using the TOPP registry suggested that the combination of risk factors and symptom progression had positive predictive value for survival/lung transplantation during the follow-up (**38**). In our treprostinil study, those allocated into WHO FC III-IV

at initiation of therapy, the mean length of survival was extremely short. The significance of functional status may be important for more than just survival, but also quality of life. In our QoL study, there was a significant difference between asymptomatic (WHO FC I) and symptomatic patients (WHO FC II-IV) in several modules. This suggests that pediatric risk stratification needs further refinements in order to have a better individualised treatment plan, similarly to the recent adult risk stratification (**3, 39**). The introduction of accelerometry (Actigraph), a daily activity test, into clinical practice may offer a new opportunity to assess functional status (**40**).

In our risk stratification evaluation study, there was not enough data available to assess the 6-minute walk test or NT-proBNP levels. The former was primarily age-biassed, the latter was funding-biassed. With regard to NT-proBNP levels, it is also worth considering the data from our treprostinil study, where in the majority of patients, NT-proBNP levels were available at the initiation of treprostinil therapy and remained very high levels throughout. Markedly elevated NT-proBNP level is a very useful marker in patients with PAH to predict a poor prognosis (**41**).

Of the non-invasive parameters, right heart echocardiographic parameters and pericardial effusion were not found to be a risk factor for poor outcome at time of diagnosis. This may be because at the time of diagnosis, the majority of patients were in good functional status (WHO FC I-II), indicating maintained right ventricular function. However, the gold standard test for accurate assessment of right ventricular function is cardiac MRI, according to the recent adult guidelines for risk stratification (**2**).

Analysing the different hemodynamic risk factors separately, PVRi proved to be the only strong predictor of the composite endpoint (death or lung transplantation). High PVRi (>20 WU*m2) at the time of diagnosis indicates very advanced PAH from a vascular point of view. Recently some centres recommend up-front triple therapy in advanced PAH. Although there is no predefined criteria for up-front triple therapy, high PVRi (>20 WU*m2) is one of the key factors for the decision (**42**).

The number of risk factors alone did not predict a poor outcome in the study population, but iPAH patients with a worse prognosis had more risk factors compared to the CHD group. Although the current guidelines do not distinguish between risk factors for the

therapeutic decision (the presence or abnormality of a single risk factor means that the patient is a high-risk group), PVRi was found to be a highly important parameter.

Subcutaneous postacyclin therapy in the high risk group

In high risk patients, the recommendation of international guidelines is the use of parenteral prostacyclin, preferably as part of combination therapy, especially in the iPAH group (**3**).

Subcutaneous treprostinil treatment in our patients was safe and well tolerated. Only one systemic adverse event (thrombocytopenia) was observed, which resolved with dose reduction. Local side effects were pain in all cases, mostly after 3-6 days of infusion site change, well tolerated with topical or oral analgesia. International experience has reported some cases of pain so severe that a switch to implantable pump therapy (continuous intravenous administration) was necessary (**43**). The latter may be a good alternative in adolescents on a stable dose.

After a relatively rapid initial dose increase, the target dose of 60-100 ng/kg/min was gradually reached. The previous US pediatric PH therapeutic guidelines for treprostinil is similar to epoprostenol and recommends a dose of 50-80 ng/kg/min (**44**), but a much wider therapeutic range is published in the literature (15-350 ng/kg/min) (**24**). The exact target dose in children remains controversial, but a continuous dose increase is recommended to reach the appropriate therapeutic goal of low risk status (WHO FC I-II, low NT-proBNP level, resolution of right heart failure, improvement in hemodynamic and/or echocardiographic parameters) (**45**).

In the small number of patients we studied, the indication for treprostinil treatment was predominantly clinical deterioration (WHO FC III-IV). Despite the long average time from diagnosis, treatment was relatively short and patients progressed rapidly to the end-stage of the disease. Importantly, these patients belonged to the iPAH group with the worst prognosis. A growing number of pediatric clinical trials demonstrate that early triple combination, and even up-front triple therapy including parenteral prostacyclin in the iPAH group with high risk, is recommended because of the poor prognosis (**42**). In the low-risk group follow-up RHC can detect progression even before development of

right heart failure and clinical deterioration, optimising the initiation of parenteral prostacyclin.

Quality of life and PAH

The risk stratification-based treatment strategy does not consider using QoL in children with PAH. Our results show that children with PAH have a poorer QoL score, as measured by the PedsQL questionnaire, than the general population of children and children with mild-to-moderate CHD and similar to children with severe CHD.

In line with previous QoL studies in PAH patients (**46**), it can be concluded that QoL and age show a strong negative correlation. This may be due to disease progression, different psychological factors of teenagers and also their frequent depressive episodes.

With regard to the risk factors determining the severity and prognosis of the disease, we were able to investigate mainly WHO functional status and echocardiographic parameters (cross-sectional study). According to the international risk stratification, WHO FC I-II is considered low risk and WHO FC III-IV is considered high risk. Only two of the children included in our study had WHO FC III status, the rest were evenly distributed between WHO FC I and II status. Thus, when compared WHO FC I with II-IV status, we found significant differences in several QoL modules. Advanced WHO FC (III-IV) was confirmed in clinical trials to be a strong predictor of prognosis and transplant-free survival (**35**), but based on our results also significantly influenced the quality of life of patients already at WHO FC II.

Of the echocardiographic parameters, TAPSE showed a significant correlation with both self and parental perception of quality of life (GCS). However, no such correlation was demonstrated in our study for left ventricular systolic eccentricity index or left ventricular end-systolic diameter (LVESD). TAPSE, as the parameter that best characterises right ventricular dysfunction, has been shown in clinical trials to be strongly correlated with survival. The association with quality of life in this study confirms that right ventricular dysfunction, which correlates closely with functional status, is a determinant of patients' well-being.

No significant difference was found for mono- versus combination PAH specific drug therapy when evaluating the QoL questionnaires. This is due to the fact that only one

patient received a triple treatment including parenteral therapy. Accordingly, our study did not answer the question of the impact of the difficulties associated with parenteral therapy on quality of life. Further clinical trials are needed, particularly in the high-risk group, to assess the QoL and the tolerability of the required parenteral therapy in children, in order to determine how parenteral therapy should be administered (subcutaneous versus intravenous).

6. Conclusions

The optimal therapy for PAH in children is a complex issue. The international therapeutic guideline is based on risk stratification, but is less able to take into account the etiology and age-specificities of PAH. As idiopathic or hereditary forms are rare in children, it is important to consider patients with PAH of different etiologies. In our risk stratification study, we clearly confirmed that children treated with CHD-related PAH have a lower mortality risk. In early risk stratification, PVRi was found to be the strongest risk factor for survival, even when adjusted for age. Combined hemodynamic risk factors did not show similar results. Among the other risk factors in our study, WHO functional status was not found to be a significant prognostic factor for survival in early risk stratification, mainly due to the study limitations. However, when comparing the WHO FC I and II-IV groups, in contrast to the international guideline, the difference was significant in terms of survival. Therefore, WHO class remains a useful tool for assessing the survival risk in PAH, but it should be stressed how difficult it is to differentiate between WHO functional classes for children. In early risk stratification, few parameters showed prognostic value for transplant-free survival, and it is therefore recommended to reassess risk stratification during follow-up on a regular basis.

Of the parenteral prostacyclins, recommended in the high-risk group, the subcutaneous treprostinil we studied, was found to be well tolerated in our patient population, with dose titration and target dose successfully achieved in the majority of cases. In the iPAH group, all patients reached the composite endpoint within 2.5 years after initiation of parenteral prostacyclin therapy at the latest. This confirms the practice of some centres to start triple therapy including parenteral prostacyclin early (up-front or rapid sequential therapy setup) and to use high doses of prostacyclin in iPAH (**42**).

Our QoL study confirmed the hypothesis that pediatric PAH is a serious disease in terms of quality of life, corresponding to the most severe cardiac malformations among heart diseases. Quality of life shows a strong negative correlation with age, which should be taken into account especially in the treatment of adolescents, for the latter, psychological support is of paramount importance. In terms of QoL, we could not prove (the low number of patients in the parenteral prostacyclin group) whether the negative effect of the limitations associated with subcutaneous pump treatment or the positive effect of the

improvement in functional status played a more important role. The negative effects of the physical limitation using a subcutaneous treprostinil pump can be reduced with an implantable device. Contrary to the risk stratification study, the QoL study confirmed the important role of TAPSE as a parameter indicating better ventricular function in the follow-up of therapy. This is why use of cardiac MRI related RV parameters in risk stratification is likely to be considered for children in the future, as it is for adults (**2**). Well-treated children are asymptomatic (WHO FC Class I) and have good RV function, and these facts are assumed to result in a better quality of life.

Limitations

Risk stratification study

Due to the retrospective data collection, some important parameters, such as NT-proBNP, were not available at baseline. Furthermore, the heterogeneous etiology and the relatively small number of patients did not allow for a complete etiology-based analysis. This was an observational study, and as with any observational study, the presence of uncontrolled confounding cannot be excluded. This is especially true, as the limited sample size only allowed the inclusion of a single potential confounder— age—in the multivariate models. Due to the low sample size (58), and the very low number of patients reaching the endpoint (19), the study had a low power to detect differences; therefore, negative results cannot be interpreted as evidence for the lack of effect.

Subcutaneous treprostinil study

Due to the low incidence of pediatric WHO FC class III-IV PAH in our centre, there was no control group or randomization of therapy in our small, observational study; hence, it is difficult to draw general conclusions from the present results. We have no patients who have reached the high (III-IV) WHO FC class and were not treated with prostacyclin. We have used prostacyclin as a bridge-to-transplant therapy (as it was a considered option). Considering our patient group size correct conrtol group (age, gender, iPAH matched) was not created. Our small descriptive study does not provide sufficient information on the issue, whether subcutaneous treprostinil is an acceptable and effective alternative to intravenous prostacyclin. However, our observations on the safety, efficacy, and

tolerability of the treatment may serve as a basis for forthcoming studies in this high-risk population of pediatric PAH.

QoL study

The cross-sectional design and the relatively low patient number of our study at the national centre is at the origin of the limitations of the study. However, all eligible PAH patients were included in the study, and the low incidence is explained by the rarity of the disease. Due to the low patient number a detailed subgroup analysis was not feasible, in particular we could not compare the parent and patient subgroup reports with each other. Regarding the established markers of disease severity, the limited number of available NT-proBNP measurements and the absence of concomitant hemodynamic catheter studies at the time of the survey did not allow establishing more precise correlations with the severity of PAH. Further, we could not find a significant difference between the intensity of therapy (monotherapy, dual or triple combination), and PedsQL-CM scores because only one patient required triple combination therapy during the evaluation.

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7. Summary

Three different studies were conducted to answer questions about the optimal treatment of PAH in children. According to international guidelines, treatment is based on risk stratification. We investigated the prognostic value of risk factors in our own patient population, confirming the important role of PVRi among hemodynamic factors. Accordingly, the role of high PVRi (>20 WU*m2) measured during RHC in early risk stratification is of particular importance. Similarly, etiology was found to be important, with better survival demonstrated in CHD-associated PAH than in the iPAH group. Due to study limitations, several risk factors could not be investigated, mainly due to age specificities. Our patients were assessed for both survival and quality of life. Poor WHO FC (II-IV) and low TAPSE were found to be the determinants of worse quality of life. At the same time, we confirmed a strong negative correlation between age and QoL, which is one of the difficulties in treating adolescents. Finally, we demonstrated good tolerability of subcutaneous treprostinil treatment in children, with rapid uptake in our practice. We recommended the initiation of early combination therapy including parenteral treprostinil, even at a good functional stage (WHO FC I-II), especially in the iPAH group. Further studies on quality of life and transplant-free survival in the different PAH patient groups with different etiologies are also recommended to develop an optimal individualised therapy.

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