Prognostic factors, treatment goals and clinical endpoints in pediatric pulmonary arterial hypertension
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Chapter 2

Current and advancing treatments for pulmonary arterial hypertension in childhood

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Chapter 2

ABSTRACT

Pulmonary arterial hypertension (PAH) is a severe and progressive intrinsic disease of the precapillary lung vasculature. Since the introduction of PAH-targeted drugs, survival of PAH patients seems to have improved. Randomized controlled trials have led to evidence-based guidelines to direct treatment in adults. However, since disease characteristics differ between adults and children, it is hazardous to simply extrapolate these guidelines to children. Moreover, pediatric data on treatment strategies and how to assess treatment response remain virtually absent. Optimal treatment strategies are highly needed to guide therapy and improve survival in children with PAH. This review provides an overview of currently available treatments of PAH and the limited efficacy and safety data in children (with the exclusion of perinatal pulmonary vascular diseases, as persistent pulmonary hypertension of the newborn). We also discuss potential treatment goals and how the available data can be translated into treatment strategies in pediatric PAH.
INTRODUCTION

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg.1 PH can be classified into five subgroups, with PH group 1 being pulmonary arterial hypertension (PAH). In contrast to the other four subgroups of PH, PAH is a progressive intrinsic disease of the precapillary pulmonary vessels characterized by unique vascular neointimal lesions.2 These result in elevation of the mPAP and pulmonary vascular resistance (PVR) leading to right-sided heart failure and ultimately death. PAH has a poor prognosis with a median survival of 2.8 years in untreated adults.3 Survival in children is believed to be even worse. Also, PAH is a rare disease, with estimated prevalence rates ranging from 6.6 to 26 cases per million adults and 20 cases per million children.4-6 In children, estimated incidence rates for idiopathic PAH (IPAH) are 0.48 to 0.7 cases per million children per year.6,7

Although the pathophysiology of PAH is not completely understood, it is believed that endothelial dysfunction is a key component.2,8 Endothelial dysfunction is associated with a decreased production of vasodilators with antiproliferative properties and an increased production of vasoconstrictors with proliferative properties. This leads to an increased pulmonary vascular muscle tone and to proliferation of vascular smooth muscle and endothelial cells. In the past decades, three major pathways have been identified in this process.9 The prostacyclin and nitric oxide (NO) pathways both lead to vasodilatation and antiproliferation. The endothelin-1 pathway has opposite effects and leads to vasoconstriction and proliferation. Three major classes of drugs interfering with these pathways have been developed: prostanoids, substituting prostacyclin, phosphodiesterase-5 (PDE-5) inhibitors, promoting the effects of NO and endothelin receptor antagonists (ERAs), inhibiting the effects of endothelin-1.

Very recently, novel drugs that interfere at different points in these pathways have either been approved or are in the stage of a Phase III clinical trial. These include the soluble guanylate cyclase stimulator riociguat that targets the NO pathway and the oral prostacyclin receptor antagonist selexipag.10,11

Based on multiple randomized controlled trials (RCTs) in adult PAH patients, evidence-based treatment guidelines have been developed and survival seems to have improved since the introduction of PAH-targeted drugs.1,12,13 Although there are similarities between adult and pediatric PAH, important differences in pathophysiology, underlying conditions, clinical presentation and outcome exist so that adult treatment algorithms cannot simply be extrapolated to children.14-16 For instance, in around 50% of children, PAH is associated with congenital heart defects that are often more complex than those in adults. PAH associated with connective tissue disease, portal hypertension or drugs is rare in children.6,17-20 Furthermore, in IPAH, syncope occurs more often in children, while heart failure is more frequent in adults.15 However, to date, there are no
specific guidelines for the treatment of pediatric PAH and its development is hampered by the lack of RCTs in children. Although available data on the treatment of pediatric PAH are accumulating, this predominantly includes observational data based on single-center studies, small select patient groups or registries. These have provided safety and tolerability data, but no controlled data on efficacy. The available pediatric data suggest that survival has also improved in children since the introduction of the PAH-targeted drugs.\textsuperscript{18,21-25} However, survival remains unsatisfactory (Figure 1) with 5-year survival rates ranging from 71 to 81\%, illustrating the high unmet need for treatment guidelines specifically for the pediatric age group.\textsuperscript{18,21-25} Optimal treatment strategies, including adequate monitoring of treatment response, are essential to guide therapy and may improve survival in children with PAH.

This review will provide an overview of the currently available treatments for PAH and the limited data on efficacy and safety in children with PAH (with the exclusion of perinatal pulmonary vascular diseases, such as persistent PH of the newborn). Further, it will discuss potential treatment goals and how the available data can be translated into treatment strategies in pediatric PAH.
OVERVIEW OF CURRENTLY AVAILABLE TREATMENTS

Supportive treatments
In the era of PAH-targeted drugs, supportive therapies should not be forgotten. Many patients with PAH receive supportive treatments during their disease course, such as anticoagulants and oxygen. Also, several general measures and lifestyle advices are often recommended and include influenza and pneumococcal immunization.16

Calcium channel blockers
Calcium channel blockers (CCBs) have been demonstrated to improve survival in a small select proportion (7%) of adults with IPAH and this has also been suggested in children.25-27 The small proportion of IPAH patients who show a positive response to acute pulmonary vasodilator testing during cardiac catheterization will sustainably benefit from CCB therapy. For a long time, the proportion of responders has been assumed to be higher in children with IPAH than in adults. However, reported values in children vary significantly (8-56%) and appear to be highly dependent on the used response criteria.24,25,27-29 In adults, responder status is usually determined according to criteria defined by Sitbon et al.26 In children, criteria defined by Barst et al., either or not modified, are often used.24,27,29 However, using the same criteria in both adults and children revealed similar proportions of responders in both age groups.28 Responders treated with CCB therapy need frequent clinical and hemodynamic reevaluation as they may become nonresponders over time and then need more advanced therapies. Due to negative inotropic effects, CCBs are advised not to be used in children <1 year of age.30 In summary, CCBs are the drug of choice for children and adults who are identified as responders according to the Sitbon or Barst criteria.1,30,31

Prostanoids
Prostacyclin is an endogenous prostanoid which is produced by vascular endothelial cells. It is a potent vasodilator that has antiproliferative and anticoagulant effects as well. Prostacyclin production is decreased in PAH. The prostanoids are synthetic prostacyclin analogs and were the first discovered class of PAH-targeted drugs. Drug-related side effects are mainly related to systemic vasodilatation and include flushing, jaw pain, diarrhea, nausea and headache. Side effects related to the administration route are significant and include line infections for intravenous (IV), site pain for subcutaneous (SC) and bronchospasm, cough and chest pain for inhaled administration.

Epoprostenol improves clinical and hemodynamic conditions as well as survival in adults and children with PAH when compared to conventional therapies.32-38 Epoprostenol therapy is possible at all ages, also in infants and toddlers. However, epoprostenol has a very short half-life and is unstable at room temperature, leading to several practi-
cal disadvantages including the need to be administered continuously intravenously through a central catheter. Also, it is generally advised to cool the epoprostenol cassette with ice packs. Intravenous administration poses the risk of line thrombosis and, more importantly, line infections that could lead to severe sepsis and death. Furthermore, these may lead to systemic embolic complications in patients with PAH associated with congenital heart disease (PAH-CHD) and a right-to-left shunt. A sudden halt of administration may lead to possibly fatal rebound PH.39

Treprostinil has a longer half-life and is chemically stable at room temperature. It can thus be administered subcutaneously, inhaled and orally as well. In adults with PAH, positive effects have been shown for SC, IV and inhaled (TRIUMPH trial) treprostinil on exercise tolerance, clinical condition and hemodynamics.40-45 Also, (a trend toward) improved survival has been reported for IV and SC treprostinil.41-43 Oral treprostinil monotherapy was shown to improve exercise capacity after 12 weeks in adults (FREEDOM-M).46 However, the addition of oral treprostinil to background therapy with a PDE-5 inhibitor, an ERA or both failed to improve exercise capacity after 16 weeks of therapy (FREEDOM C1/C2 trials).47,48 Data regarding treprostinil therapy in children are limited. Because of the pain and inflammation at the puncture place, SC therapy has been thought not to be feasible in children. However, two small studies that included 8 and 29 children showed improvements in clinical condition and hemodynamics after add-on therapy with SC and inhaled treprostinil, respectively, without significant side effects. Both drugs appeared to have acceptable safety profiles.49,50

Beraprost was initially reported to improve clinical condition and hemodynamics in adults with PAH (ALPHABET trial), but these effects did not persist after a longer period of follow-up.51-53

Iloprost is mainly used as an inhaled prostanoid. Beneficial effects of inhaled iloprost as mono- or add-on therapy, which persisted until at least one year after treatment initiation, have been demonstrated in adults with PAH (AIR and STEP trials).54-56 Some clinical improvements were reported in a proportion of children in two small single-center studies.57,58 Switching to or addition of IV iloprost in adult patients, who clinically deteriorated on non-IV therapy, resulted in clinical and hemodynamic improvements only in a subgroup of these patients.59-61

Endothelin receptor antagonists

Endothelin-1 serum levels are increased in PAH patients.62 Two receptors mediate endothelin-1 in humans: endothelin-A and endothelin-B receptors.63 Both receptors are found in pulmonary vascular smooth muscle cells, where they promote vasoconstriction, inflammation and proliferation. Endothelin-B, however, is also present in pulmonary endothelial cells, where it mediates vasodilatation and activates antiproliferative agents. ERAs block these receptors, either both of them or the endothelin-A receptor
selectively, and thereby inhibit the effects of endothelin-1. An advantage of selective over dual blocking or the other way around has not been demonstrated. The major side effects of ERAs are liver enzyme elevation, peripheral edema and a decrease in hemoglobin levels. ERAs for PAH are given orally and there are no major side effects related to the administration route.

*Bosentan* is a dual receptor antagonist that has been demonstrated to improve 6-min walk distance (6MWD), World Health Organization functional class (WHO-FC) and time to clinical worsening in adults with PAH (BREATHE-1 trial). Several uncontrolled pediatric studies, including 19-101 children, suggested similar effects. Importantly, bosentan appeared to be well tolerated and safe in children and a pediatric formulation is available. Elevation of liver enzymes appears to occur less frequently in children than in adults (3% versus ~10%). Nonetheless, regular testing remains necessary as elevations require dose adaptation or discontinuation of bosentan.

*Ambrisentan* is a selective endothelin-A receptor antagonist that has demonstrated effects comparable to bosentan (ARIES trials). A retrospective study in 38 children suggested that ambrisentan may have beneficial effects in a subset of children with PAH. Furthermore, ambrisentan may have a favorable safety profile compared to bosentan, including less liver function abnormalities and less drug interactions.

*Macitentan*, a dual receptor antagonist with sustained receptor binding and increased tissue penetration, was recently shown to significantly reduce morbidity when compared to placebo in 742 PAH patients aged >12 years (SERAPHIN trial). Clinical and hemodynamic parameters improved after 6 months of therapy compared to placebo. Macitentan had a favorable safety profile with little occurrence of liver enzymes elevation and peripheral edema. To date, no data are available in children.

**PDE-5 inhibitors**

PDE-5 inactivates cyclic guanosine monophosphate through which NO mediates its vasodilatory and antiproliferative effects. The PDE-5 inhibitors inhibit the actions of PDE-5, and thus increase the effects of available NO. The most common side effects are related to systemic vasodilatation and include headache, flushing and epistaxis. In general, PDE-5 inhibitors for PAH are given orally and there are no major side effects related to the administration route.

*Sildenafil* has been shown to have beneficial effects in adults with PAH that persist up to 3 years after start of therapy (SUPER trials). Also, sildenafil treatment was well tolerated. STARTS-1 was the first randomized, double-blind, placebo-controlled study ever in children with PAH. Although the beneficial effect on the primary endpoint of the study, peak oxygen consumption on cardiopulmonary exercise testing (CPET), just failed to reach statistical significance, the results showed improvements in hemodynamics in the medium- and high-dose sildenafil-treated groups. The recently published results
of the subsequent STARTS-2 trial suggested worse survival in children receiving high doses of sildenafil. However, the data were not conclusive. This is illustrated by the fact that these data caused the United States Food and Drug Administration to recommend against the use of sildenafil in children, whereas the European Medicines Agency approved the use of sildenafil in children with a warning against high doses of sildenafil. The American Pediatric Pulmonary Hypertension Network stated that ‘although we believe that low doses of sildenafil are likely to be safe in pediatric PAH and we support the EMA finding, further studies should carefully examine its role in the long-term therapy of children.’

**Tadalafil** has been demonstrated to improve exercise tolerance and hemodynamics and to lead to better quality of life and increased time to clinical worsening after 16 weeks of therapy in treated adults compared to placebo (PHIRST trial). Improved exercise tolerance was maintained after another 52 weeks. Tadalafil treatment was safe and well tolerated. Pediatric data regarding tadalafil are scarce. One retrospective, single-center cohort study was performed that included 33 children who either transitioned from sildenafil to tadalafil (29 patients) or received tadalafil as initial PDE-5 inhibitor therapy (4 patients). Transition to tadalafil improved mPAP, indexed PVR and pulmonary-to-systemic vascular resistance ratio, while exercise capacity, brain natriuretic peptide (BNP) and cardiac index did not significantly change. Clinical and hemodynamic conditions tended to improve in the 4 patients who received initial tadalafil therapy. Tadalafil appeared to be safe and well tolerated.

**Vardenafil** is a new PDE-5 inhibitor that has been shown to improve exercise tolerance and hemodynamics after 3 and 14 months when compared to baseline and after 12 and 24 weeks when compared to baseline and placebo in 45 and 66 adult PAH patients, respectively (EVALUATION trial). Side effects were mild and mostly transient. To date, no data are available in children.

**Novel drugs**

**Riociguat**, a soluble guanylate cyclase stimulator, is a novel drug that acts more upstream in the NO pathway than the PDE-5 inhibitors. Riociguat increases cyclic guanosine monophosphate availability by directly stimulating soluble guanylate cyclase. Its actions can be synergistic with NO, but it can also act completely independent of NO. Riociguat improved exercise capacity, clinical condition and hemodynamics in PAH patients after 12 weeks of therapy compared to baseline and placebo (PATENT trial). To date, no data are available in children.

**Selexipag** is an oral selective prostacyclin receptor agonist. A Phase II study including 43 adult PAH patients on stable background therapy showed that PVR improved after 17 weeks of addition of selexipag and that it was well tolerated. Phase III clinical trial results are currently pending (GRIPHON trial). To date, no data are available in children.
Imatinib is a tyrosine kinase inhibitor that was initially developed for the treatment of chronic myeloid leukemia. It inhibits vascular smooth muscle cell proliferation and hyperplasia. Thus, unlike the previously described drugs targeting the three major pathways, imatinib has mainly antiproliferative effects. Imatinib was shown to have beneficial effects in patients with severe PAH. However, more discontinuations and serious adverse events (including subdural hematoma) were reported in the imatinib group compared to placebo. Consequently, the authorization application for imatinib in PAH was withdrawn. There are no data regarding imatinib in pediatric PAH.

Several novel drugs targeting newly identified pathways in the pathogenesis of PAH are currently under investigation and may be promising drugs for the future. These include rho kinase inhibitors targeting the Rho/Rho-kinase signaling pathway, which influences many cellular actions including apoptosis, inflammation and vasoconstriction, and endothelial progenitor cells targeting regeneration and repair of damaged lung microvasculature.

Combination therapies
The rationale behind combination therapy is that the PAH-targeted drugs target three different pathways and that simultaneous targeting of two or three of these pathways may lead to a greater beneficial effect than targeting only one pathway. The current guidelines for the treatment of adults with PAH summarize options for treatment initiation. The level of evidence and recommendation for the use of combination therapies has significantly improved since controlled data on such use are becoming increasingly available, although this evidence is almost exclusively based on adult studies.

Since the early 2000s, various studies on the effects of combination or add-on therapy in PAH have been performed.

The combination of an ERA and a PDE-5 inhibitor has been shown to (tend to) improve exercise capacity, functional status and hemodynamics in adults compared to monotherapy with one of these drugs. Also, the addition of macitentan to PDE-5 inhibitor therapy improved time to the combined endpoint, including worsening of PAH, lung transplantation (LTx), escalation to IV or SC prostanoids and death (SERAPHIN trial). Combining both classes appeared to be safe and well tolerated in all studies. Add-on riociguat to ERA or non-IV prostanoid therapy was shown to be beneficial and safe in the PATENT trial.

Combining prostanoids with either ERAs or PDE-5 inhibitors has been studied in different compositions. Add-on sildenafil therapy in adults receiving long-term IV epoprostenol improved clinical and hemodynamic conditions and time to clinical worsening (PACES trial). Add-on therapy with inhaled treprostinil or inhaled iloprost to ERA and/or PDE-5 inhibitor therapy was studied in adults who did not improve on oral therapy alone (TRIUMPH and STEP trials). Both were shown to improve exercise capacity,
Furthermore, inhaled iloprost was shown to prolong time to clinical worsening and the beneficial effects of inhaled treprostinil were shown to persist for 24 months. Beneficial results have also been reported for the addition of bosentan to SC treprostinil therapy.

Thus, several studies have shown beneficial effects of add-on combination therapy in adult PAH patients who did not adequately respond to monotherapy. Little research has been done regarding this subject in children. A recently published report, including 275 children, showed that children who received combination therapy during the study period had better survival compared to children who received monotherapy, independent of disease characteristics at baseline. Another recent report, including 24 children, showed that the addition of sildenafil to bosentan improved WHO-FC and 6MWD in children who clinically deteriorated on bosentan mono therapy. Survival seemed to improve in the children who received add-on sildenafil therapy compared to those who remained on bosentan therapy alone. Add-on therapy with inhaled or SC treprostinil was shown to improve clinical and hemodynamic conditions in children with severe PAH. These results point in the same direction as those obtained in adult studies, supporting the beneficial effects of add-on combination therapy in pediatric PAH.

Although combination therapy seems to be efficacious in both adults and children with PAH, it remains unclear when and how to start combination therapy and what disease characteristics could guide decisions regarding therapy escalation.

Nondrug treatments

Nondrug treatments could be considered to preserve cardiac output and to reduce the right ventricular (RV) workload. They could serve as a treatment option to relieve symptoms or as a bridge to LTx.

Balloon atrial septostomy (BAS) is used in patients with IPAH and end-stage disease, recurrent syncope or both. As syncope is more frequent in the pediatric age group, BAS could be more often of use in children than in adults. BAS is believed to lead to an increase of left ventricle preload and cardiac output at the cost of a decrease in systemic arterial oxygen saturation. This overall is assumed to result in increased systemic oxygen transportation. Several small uncontrolled studies including adults and/or children reported improvements in clinical and hemodynamic conditions. BAS has been suggested to improve survival as well, increasing the chance of receiving donor lungs. BAS requires an invasive procedure, which brings concomitant risks, especially in this vulnerable population. In patients with severely elevated right atrial pressure (RAP), the mortality rate increases due to potential major right-to-left shunting with life-threatening hypoxemia. Thus, it has been advised not to wait with BAS until this hemodynamic condition develops.
**Potts shunt**, a (direct) anastomosis between the left pulmonary artery and the descending aorta, forms an alternative way to create a pulmonary-to-systemic shunt and, when compared to BAS, has the advantage of directly relieving the right ventricle. This technique is suitable for patients with suprasystemic pulmonary pressures and can also be used in patients with concomitant severely elevated RAP. The decrease in oxygen saturation will only occur in the lower body half. Two case reports of both two children and one retrospective multicenter study of eight children with end-stage IPAH showed improved functional and exercise capacity, lower plasma levels of BNP and improved RV function in both the short- and longer-term.\(^{108-110}\) However, postoperative mortality in this early experience was reported to be 25% in the multicenter study, illustrating the high risk of invasive procedures in PAH patients. Further research including more patients is essential to evaluate the short- and long-term effects of this palliative procedure.

**Aortic banding** is based upon the theory of ventricular-ventricular interaction, in which right heart disease alters left ventricular function and vice versa. A recent experimental study including 23 rabbits showed that aortic constriction in a model of chronic RV pressure overload resulted in improved biventricular function and myocardial remodeling.\(^{111}\) To date, no studies in humans exist and its possible value in (pediatric) patients with PAH remains to be elucidated.

**(Heart-)LTx** remains the treatment of choice for end-stage PAH despite maximal therapy. As the heart has the ability to recover and re-remodel to normal function and dimensions, bilateral LTx is most frequently performed. In children, IPAH is the second most common indication for LTx.\(^{112}\) Given the high risk and major consequences of the procedure, LTx is only indicated in patients with progressive and severe PAH despite maximal medical therapy. Several small studies including children with IPAH that underwent bilateral LTx showed improved WHO-FC, improved RV function and improved survival, with a median survival that ranged from 45 to 70 months.\(^{113-115}\) Reported survival was comparable or improved compared to LTx in children with cystic fibrosis.\(^{112}\) Whether a child is eligible for transplantation and what the optimal timing is remains unknown and is mostly determined by the center’s expert opinion and donor organ availability. Although medical treatment options are expanding and seem to be beneficial, medical therapy should not lead to (too) late listing for LTx.

In summary, over the past 15 years, many RCTs showed that PAH-targeted drugs are efficacious in the treatment of PAH in adult patients. Although mainly uncontrolled, observational studies exist in children with PAH, the available data suggest comparable effects. The available PAH-targeted drugs appear to have acceptable safety and tolerability profiles also in children, except for sildenafil in which this is a subject of debate. Combination therapy with PAH-targeted drugs that act on different pathways could lead to additional beneficial clinical effects, also in pediatric PAH. Novel drugs targeting exist-
ing or newly discovered pathways in the pathogenesis of PAH are being developed and will hopefully further improve quality of life and survival in pediatric PAH. Furthermore, nondrug treatments are available for children and are believed to have a place in treatment strategies for children with PAH.

**TREATMENT STRATEGIES**

Although the development of novel drugs for the treatment of PAH is of great importance, knowledge on how to use the various drugs combined in optimal treatment strategies is at least as important. To improve survival and optimize quality of life in patients with PAH, relevant considerations include choice of drugs, timing of therapy initiation and when and how to use combination therapy. For example, guidelines recommend combination therapy ‘in case of inadequate clinical response’. However, how should inadequate clinical response be defined?

A goal-oriented treatment strategy is now recommended to guide therapy in adult PAH patients. Instead of reacting on deterioration of a patient’s clinical condition, the physician aims to reach a predefined improvement in clinical condition. Thus, patients who start therapy are supposed to reach certain goals. If these goals are not met within 3–6 months, therapy should be escalated. For such a strategy, it is essential to have reliable, validated and clinically meaningful treatment goals that are applicable in all patients and that can be obtained without disproportional risks.

The treatment of patients with PAH aims at improving quality of life and survival. Therefore, a treatment goal could be a measure that represents improved quality of life, for instance relieve of symptoms or improvement of exercise capacity. Also, a treatment goal could be a clinical measure that represents a decrease in the chance of an outcome event, such as death or LTx. Thus, a variable that serves as a treatment goal either directly reflects quality of life or meets the following criteria for a surrogate for outcome: has a strong correlation with outcome, values can be influenced by therapy and treatment-induced changes reflect a change in outcome. Thus, a variable that serves as treatment goal is not simply a predictor of outcome. It should additionally be influenced by therapy. To illustrate this, although patient characteristics as age and sex are reported to predict outcome, it is obvious that these are no suitable treatment goals. The third requirement for a treatment goal indicates that a treatment-induced change in the variable should reflect a change in outcome. For example, improved WHO-FC after 6 months of therapy should be associated with improved survival. Follow-up assessments are therefore necessary.

Several clinical, biochemical and hemodynamic variables have been identified as predictors of outcome both in adults and children with PAH (Table 1). However, data
on the predictive value of treatment-induced changes in these predictors are scarce. Few observational studies regarding treatment-induced changes in adults have been published.\textsuperscript{121-124} Very few data are currently available in children. Although the concept of goal-oriented treatment seems reasonable and beneficial, these variables should be sufficiently validated as treatment goals in the relevant patients, so also in children with PAH.

**Table 1.** Evidence for the Prognostic Value of Potential Treatment Goals in Children with Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Prognostic implications at baseline (Ref.)</th>
<th>Prognostic implications at follow-up (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical condition</strong></td>
<td></td>
</tr>
<tr>
<td>WHO-FC</td>
<td>7, 21-23, 25, 126, 127</td>
</tr>
<tr>
<td>6MWD</td>
<td>126</td>
</tr>
<tr>
<td>CPET</td>
<td>-</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
</tr>
<tr>
<td>(NT-pro)BNP</td>
<td>23-25, 36, 141-143</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>126, 146, 147</td>
</tr>
<tr>
<td>CMR</td>
<td>148</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
</tr>
<tr>
<td>mRAP</td>
<td>25, 27</td>
</tr>
<tr>
<td>PVRi</td>
<td>22, 24, 25, 27, 126, 131</td>
</tr>
<tr>
<td>mPAP/mSAP</td>
<td>23, 25, 28, 127</td>
</tr>
<tr>
<td>CI</td>
<td>23-25, 27</td>
</tr>
<tr>
<td>Pulsatile components of RV afterload</td>
<td>127, 131</td>
</tr>
</tbody>
</table>

6MWD, six-minute walk distance; CI, cardiac index; CMR, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; mPAP/mSAP, mean pulmonary-to-systemic arterial pressure ratio; mRAP, mean right atrial pressure; (NT-pro)BNP, (N-terminal pro) brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RV, right ventricular; WHO-FC, World Health Organization functional class.

Current treatment goals in adult patients, as recently proposed at the 5\textsuperscript{th} World Symposium for Pulmonary Hypertension (WSPH) held in Nice 2013, to optimize prognosis in patients with PAH include WHO-FC I-II, near-normal or normal RV size and function on echocardiography or cardiac magnetic resonance (CMR), RAP <8 mmHg and cardiac index >2.5 to 3.0 l/min/m\textsuperscript{2} on cardiac catheterization, 6MWD >380 to 440 m, peak oxygen consumption >15 ml/min/kg on CPET and normal plasma levels of N-terminal pro brain
natriuretic peptide (NT-proBNP) or BNP. Based on the strength of expert opinion, the pediatric task force of the 5th WSPH proposed a treatment algorithm for children with IPAH in which patients are characterized using a risk profile based on proposed pediatric treatment goals. An adapted version of this risk profile is shown in Table 2.

<table>
<thead>
<tr>
<th>Lower risk</th>
<th>Treatment Goals</th>
<th>Higher risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Progression of symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>I, II</td>
<td>WHO functional class</td>
<td>III, IV</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>Serum BNP/NT-proBNP</td>
<td>Significantly elevated, rising level</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Severe RV enlargement/dysfunction</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Systemic CI &gt;3.0 L/min/m²</td>
<td>Hemodynamics</td>
<td>Systemic CI &lt;2.5 L/min/m²</td>
</tr>
<tr>
<td>mPAP/mSAP&lt;0.75</td>
<td></td>
<td>mPAP/mSAP&gt;0.75</td>
</tr>
<tr>
<td>Acute vasoreactivity</td>
<td></td>
<td>RAP &gt;10 mmHg</td>
</tr>
<tr>
<td>Stable &gt;450 m</td>
<td>6MWD*</td>
<td>≤350 m or decreasing</td>
</tr>
</tbody>
</table>

*Although the 6MWD was not proposed as treatment goal by the WSPH pediatric task force, maintaining of or improving to an adequate 6MWD can be regarded as clinically meaningful in pediatric PAH, as improved exercise capacity is believed to improve quality of life. 6MWD, six-minute walk distance; BNP, brain natriuretic peptide; CI, cardiac index; mPAP/mSAP, mean pulmonary-to-systemic arterial pressure ratio; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PVRi, pulmonary vascular resistance index; RV, right ventricular. Adapted with permission from [30].

In the following section, variables that may serve as treatment goals in children with PAH will be discussed and the relevant evidence will be reviewed.

Clinical characteristics of PAH in children include symptoms, such as dyspnea at rest and/or during exercise, exercise intolerance, syncope, fatigue and chest pain, that could greatly impact quality of life. Reducing these symptoms is clinically relevant, will improve quality of life and thus can be regarded as a valid treatment goal in children with PAH. Children with PAH may show failure to thrive. Lower age-normalized scores for height and weight have been suggested to correlate with worse survival. However, this could not be confirmed in two other cohorts. Furthermore, no catch-up growth after treatment initiation was found, which potentially disqualifies growth, or age-normalized scores for height and weight, as treatment goals.

Although a correlation between syncope and survival has not been confirmed in several pediatric studies, the occurrence of syncope or its persistence after treatment
initiation is regarded as a serious sign of disease and according to current expert opinion requires escalation of therapy.\textsuperscript{7,24,30}

\textit{WHO-FC} is a non-invasive, subjective assessment of a patient’s clinical condition using the occurrence of symptoms at different levels of activities. WHO-FC, both at baseline as well as after treatment, has been shown to strongly correlate with survival in adult PAH patients.\textsuperscript{121-123} It therefore represents a useful treatment goal to guide therapy in adults. WHO-FC can be difficult to assess in infants and young children as it will be based on the observation and impression of caregivers. An age-adjusted estimation of a child’s physical activity in relation to its peers may help to accurately determine WHO-FC. Despite this apparent limitation, several pediatric studies have shown WHO-FC to be a strong predictor of outcome that could be affected by therapy.\textsuperscript{7,21-23,25,125-127} A functional classification system specifically designed for children has been proposed but has not been validated yet.\textsuperscript{128} Overall, WHO-FC is an easy and freely obtainable parameter reflecting clinical condition also in children. As in adult PAH, the WSPH pediatric task force proposed reaching or maintaining WHO-FC I or II as a treatment goal in pediatric PAH.

\textit{Six-minute walk distance} is widely used to assess clinical condition in adult PAH. It has served as primary endpoint in most RCTs. A meta-analysis recently showed that changes in 6MWD may not reflect changes in outcome.\textsuperscript{129} The use of 6MWD in children is limited due to developmental restrictions: infants do not walk, young children may be distracted during the test and developmental delays may affect the test results. In general, it is a reliable and reproducible test that can be performed from an age of 7 years.\textsuperscript{130} However, many children are younger than 7 years at diagnosis.\textsuperscript{6,7,22} The predictive value of 6MWD for outcome in children with PAH is unclear and available data from various observational studies are contradictory on this point.\textsuperscript{25,126,131} Nevertheless, as in adults, 6MWD can be improved by therapies in children with PAH.\textsuperscript{6,7,22,57,65,66,102} Since improved exercise capacity is believed to improve quality of life, maintaining of or improving to an adequate 6MWD can be regarded as a valid treatment goal in pediatric PAH.

\textit{Cardiopulmonary exercise testing} has been shown to predict survival in adults with PAH.\textsuperscript{132,133} Treatment-induced changes have not been studied. In young children, the use of CPET is also hampered by limited feasibility due to developmental issues. Reference values are available for children from an age of 6-8 years.\textsuperscript{134,135} Peak oxygen consumption was shown to correlate with mPAP and PVR in 40 children with PAH.\textsuperscript{136} Also, CPET has been suggested to provide complimentary information to the 6MWT.\textsuperscript{137} A possible correlation between CPET and survival in children with PAH has not been studied. Overall, its value in a goal-oriented treatment strategy in children remains unknown.

\textit{NT-proBNP} and \textit{BNP} are biomarkers related to RV dysfunction, which is one of the most important predictors for survival in PAH.\textsuperscript{3} Both in adults and children, plasma levels of (NT-pro)BNP have been shown to strongly correlate with survival.\textsuperscript{23,25,36,138-143} Recently, treatment-induced changes in NT-proBNP were shown to be associated with
a change in survival in adults, making NT-proBNP a valid treatment goal. In children with PAH, changes in (NT-pro)BNP levels have been correlated with changes in WHO-FC, 6MWD and hemodynamics. Although the correlation between treatment-induced changes of (NT-pro)BNP and survival has not been studied yet, the WSPH pediatric task force proposed reaching (near-)normal levels of (NT-pro)BNP as treatment goal and advised (NT-pro)BNP to be part of the regular follow-up in pediatric PAH.

**Echocardiography and CMR** are both noninvasive methods to assess RV function. In adults and children with PAH, echocardiographic and CMR parameters at baseline have been associated with survival. Furthermore, treatment-induced changes in CMR parameters were shown to predict survival in adult patients. Although data are promising, they remain currently limited and further research is necessary to determine the value of echocardiography and CMR in guiding treatment in PAH patients. According to the WSPH pediatric task force, the findings of severe or progressive RV dysfunction or pericardial effusion dictates escalation of therapy.

**Hemodynamic parameters** are objective and can be obtained at any age. In adults, hemodynamics at baseline have been shown to predict survival. Treatment-induced changes in cardiac index and mixed venous oxygen saturation were recently reported to correlate with changes in survival, supporting their use as treatment goals. Hemodynamic variables, such as RAP, indexed PVR, cardiac index and mean pulmonary-to-systemic arterial pressure ratio, have been associated with survival in the pediatric age group. Furthermore, initiation of therapy has been shown to improve hemodynamics. Recently, pulsatile components of RV afterload were shown to predict survival in children with PAH, as in adults. Although it seems reasonable to assume that treatment-induced improvements in hemodynamics will lead to a better outcome, this remains to be demonstrated in pediatric PAH. Furthermore, obtaining invasive hemodynamics by cardiac catheterization often requires the use of sedation or general anesthesia in childhood, which comes with associated risks. Cardiac catheterizations in pediatric PAH carried out in specialized centers are reported to have a complication rate (major complications) of 4–6%. Nevertheless, the WSPH pediatric task force proposed hemodynamic variables as potential treatment goals. Many, but not all, expert centers for pediatric PAH practice a strategy of repeated cardiac catheterizations during follow-up, with the rationale that the risks of cardiac catheterization, if minimized via adequate expertise of the treatment team, will be outweighed by the benefits of optimizing therapy and improvement of outcome.

In summary, although outcome in pediatric PAH has improved since the introduction of PAH-targeted drugs, survival of children with this disease is still unsatisfactory. Improvement in treatment success is highly needed and waiting for clinical deterioration to escalate initiated therapy may not be the way to go. Therefore, goal-oriented treatment strategies are currently adopted in the management of pediatric PAH. Taking
into account the paucity of data on treatment goals in children with PAH, the WSPH pediatric task force agreed on recommending several variables to serve as treatment goals, including clinical symptoms, WHO-FC, (NT-pro)BNP, RV imaging and invasive hemodynamics. However, proper validation of these variables as treatment goals remains to be done.

EXPERT COMMENTARY

Although several PAH-targeted drugs have been developed and their efficacy has been demonstrated, outcome in children with PAH remains poor. Therefore, there is a high, but unmet, need for better treatment strategies specifically for children. Knowing how to adequately assess treatment response and when and how to escalate therapy is essential. Emerging evidence is becoming available that children with PAH may benefit from adequate monitoring of treatment response and more aggressive treatment regimens with escalation to combination therapy.

Ideally, pediatric data for evidence-based guidelines, that is, RCTs, should be collected. However, controlled trials in pediatric PAH were and will be hampered by difficulties. First, it is challenging to reach appropriate study sizes due to the rarity and heterogeneity of the disease. Second, the widespread pediatric use of currently available PAH-targeted drugs complicates study designs. Several PAH-targeted drugs are regarded ‘standard of care’, while not approved for children. Third, there is a lack of validated endpoints in pediatric PAH, including the nonacceptance by the regulatory authorities of invasive hemodynamics as endpoint. Therefore, much of the pediatric data will have to be derived from clinical registries and cohorts that collect patient and treatment characteristics and outcome data. A standardized follow-up, with predefined variables and timepoints, would be very helpful. Registries may be multicenter, multi-country center-based, such as the TOPP and REVEAL registries. They may also be based on national cohorts, such as the Dutch and United Kingdom national service registries. Furthermore, there are single-center registries. All these registries, each with its unique design and thereby having its own merits and disadvantages, and providing mostly observational data, will have to clearly define their aims and collect relevant data. Only then, registries will be able to contribute to the actual questions that arise in defining the optimal management of children with different types of PAH in the coming future.

One of these questions is whether children with IPAH and children with PAH-CHD should be treated equally. Most of the studies regarding PAH-specific therapies have been performed in patients with IPAH. Nevertheless, an increasing amount of data is becoming available showing that these drugs, perhaps with the exception of CCBs, have similar effects in both groups. The same holds for clinical predictors of outcome. Further-
more, although survival of patients with PAH-CHD has long been assumed to be more favorable than survival of patients with IPAH, recent data indicate that in childhood, survival is equally poor in both types of PAH. Based on current knowledge, the authors feel that there is no indication to treat children with PAH-CHD according to different treatment algorithms than children with IPAH. Nevertheless, practical issues should be considered for the individual patient, such as the use of central catheters in patients with a right-to-left shunt.

Importantly, defining clinically relevant treatment goals that correlate with long-term outcome has emerged as one of the most critical tasks. Effort should be put in establishing and validating these treatment goals, which will help to guide therapy and improve the currently unsatisfying outcome in pediatric PAH.

FIVE-YEAR VIEW

In the next five years, treatment options for patients with PAH will likely expand. More drugs, targeting new pathways, will become available and have to be evaluated in RCTs. ‘Smart-design’ controlled trials should be designed to collect evidence for efficacy in the pediatric PAH population. Also, the value of nondrug treatments should be established within the setting of drug treatment. Especially the role of the Potts shunt in short- and long-term outcome of pediatric PAH will have to be investigated. Since experience in this technique is limited and patient numbers are small, a multicountry registry for this intervention could be very valuable.

In the coming years, data from newly or redesigned registries will become available that will allow for the assessment and validation of the recently proposed treatment goals and the identification of new treatment goals. With these, evidence-based guidelines that define how to accurately monitor treatment response and escalate therapy will be developed also for children. Finally, novel therapies directed toward the reversal of RV dysfunction in PAH may become available.
REFERENCES


