Pediatric pulmonary arterial hypertension: on the eve of growing up

Johannes M. Douwes and Rolf M.F. Berger

Purpose of review
Current recommendations for diagnosis and treatment of pulmonary arterial hypertension (PAH) during childhood are expert opinion based, because of lacking pediatric data. In recent years, however, important pediatric data have emerged on PAH.

Recent findings
PAH in children shows similarities as well as differences compared to adults. Neonates and children know specific clinical presentations and a hemodynamic profile that differs from adults with PAH. Children identified as acute vasodilator responders according to the criteria proposed for adults rather than the pediatric criteria have better outcome when treated with calcium channel blockers. For nonresponders, combination PAH-targeted therapy leads to improved outcome compared to monotherapy. In pediatric PAH, WHO functional class, N-terminal pro-brain natriuretic peptide and tricuspid annular plane systolic excursion were identified as surrogates for survival and therefore qualify to be treatment goals in a goal-oriented treatment strategy.

Summary
In order to refine current pediatric treatment guidelines, data on efficacy of specific treatment regimens and strategies are needed. The recently validated composite endpoint of clinical worsening allows for trials that will provide these data. For the first time, evidence-based treatment goals have been identified that will allow for a goal-oriented treatment strategy. Furthermore, various prognostic predictors have been identified that may prove treatment goals in future.

Keywords
endpoint, pediatric pulmonary hypertension, prognosis, pulmonary arterial hypertension, treatment

INTRODUCTION
Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disease with a detrimental prognosis. PAH in childhood shares similarities with PAH in adults, but also differs in presentation, epidemiology and disease course. Adult data on PAH are therefore not directly applicable to pediatric patients. Because of a historical lack of pediatric data, no evidence-based pediatric treatment guidelines could be designed. Instead, recently, three sets of recommendations for diagnosis and treatment of pediatric PAH have emerged that are far from consistent in their recommendation and apparently based on selective expert opinions rather than on consensus, illustrating the high clinical need for supportive data in this population.

In recent years, pediatric data have become available that will help to better understand PAH in childhood and to develop in the near future pediatric recommendations that are more evidence based. In the absence of randomized clinical trials in pediatric PAH, these data come mainly from observational and registry studies, a design that in a rare disease may be an effective source for important data on epidemiology, clinical course, current medical practice and even treatment effects. Especially large well-designed patient registries such as the TOPP-registry, the pediatric REVEAL data and the Dutch national registry with prospective, standardized...
KEY POINTS

- Children with PAH who respond to vasodilator challenge should be treated with CCBs.
- WHO functional class, NT-proBNP and TAPSE have been identified as surrogate parameters for survival that can serve as treatment goals in pediatric PAH.
- A composite endpoint including death, lung transplantation, nonelective PAH-related hospitalization, initiation of IV prostanoids and functional deterioration has been identified as a feasible endpoint for clinical trials in pediatric PAH.
- Upfront or early combination therapy may further improve outcome of pediatric PAH.

follow-up for pediatric pulmonary hypertension have brought substantial progress to the field.

EPIDEMIOLOGY

PAH during childhood is mostly idiopathic PAH (iPAH) or associated with congenital heart disease (PAH-CHD) [1]. The latter represents a group of heterogeneous conditions, currently classified according to a shunt-based classification [2,3]. Recently, it has been shown that 11% of pediatric cases cannot be classified according to this classification for PAH-CHD [4]. For instance, PAH after neonatal correction of transposition of the great arteries by arterial switch operation is identified as such a specific disease entity, which may have a distinct pathophysiology and clinical course, but cannot be classified using the current shunt-based classification [5].

PAH in children is characterized by a preserved cardiac index and mean right atrial pressure, despite highly elevated PVRi [6]. The hemodynamic characterization of PAH in children therefore differs from that in adults, indicating better preservation of right ventricular function at diagnosis in children compared to adult PAH patients.

It has long been thought that children have a higher prevalence of acute vasodilator response, because of a more responsive pulmonary arterial vascular bed than adults. Recent evidence, however, demonstrates that acute vasodilator response in children with PAH is comparable to adults with the disease, both regarding occurrence rate and predictive value for effect of calcium channel blocker (CCB) therapy. These data thereby clear the argument for specific pediatric acute vasodilator response criteria [7,8]. When using the vasodilator response criteria proposed for adult patients, 15% of children with iPAH could be identified as acute responder and these children were shown to have an excellent outcome when treated with CCB [3,7]. Also, it was shown that no potential pediatric responders with good outcome on CCB therapy were missed using these criteria. Considering the substantial proportion of acute responders and the clear outcome benefit, acute vasodilator response testing and treatment of responders with CCB should be standard practice for children with idiopathic and familial PAH.

Current data on pediatric pulmonary hypertension largely focus on PAH, which is therefore the focus of this review. However, growing interest in pulmonary hypertension associated with chronic lung disease of infancy or bronchopulmonary dysplasia (BPD) is noteworthy. Because of improved perinatal care over the past decades, the survival of preterm and (very) low birth weight infants has increased, leading to an increased incidence and evolving phenotype of BPD [9]. It has been acknowledged that children with BPD who develop pulmonary hypertension are at greater risk of poor outcome. Recently, risk factors for the development of pulmonary hypertension in BPD patients, both maternal and perinatal, have been identified, including ventilation duration, duration of hospital stay, oligohydramnios, birth weight, being small for gestational age, sepsis, gestational age and BPD severity [10,11]. However, recent reviews of literature show that there is a lack of knowledge on the prevalence, clinical course, optimal detection moment, screening protocol, treatment and long-term outcome of BPD-associated pulmonary hypertension [11–13]. Prospective cohort studies are necessary to investigate the occurrence and disease development over time, from birth until longer term follow-up, in order to overcome this lack of data.

PULMONARY ARTERIAL HYPERTENSION-TARGETED THERAPY

According to current treatment recommendations, children with PAH who are not acute vasodilator responders are treated according to a risk stratification composed of several indicators of disease severity [2,14]. Patients stratified as lower risk group are advised to be started on monotherapy of oral endothelin receptor antagonist, oral phosphodiesterase type 5 inhibitor or inhaled prostanoids. Higher risk patients are advised to be started on either intravenous prostanoids or early combination therapy [2,14]. After treatment initiation, therapy is advised to be intensified by upscaling to dual or triple therapy upon either clinical deterioration or
upon not reaching clinical improvement (goal-oriented treatment strategy).

Data from the large international TOPP-registry showed that currently 73% of children with PAH are initially treated with PAH-targeted therapy. Most patients are started on PAH-targeted monotherapy, whereas upfront dual and triple therapy were administered less frequently [15]. In 2003, BREATHE-3 was the first study to suggest beneficial effect of adding bosentan to epoprostenol background therapy in children with PAH [16]. In 2011 and 2012, two reports suggested that adding subcutaneous and inhaled treprostinil to PAH background therapy is effective [17,18]. More recently, sildenafil add on therapy to bosentan monotherapy was shown to improve disease severity and outcome compared to persistent monotherapy [19]. Furthermore, results of a large multicenter study suggested that treatment with combination therapy is associated with improved outcome compared to monotherapy [20]. Recent evidence therefore indicates that combination therapy results in improved outcome for pediatric PAH. Considering that outcome of pediatric PAH remains poor despite the availability of several PAH-targeted therapies, the authors feel that this evidence provides sufficient support to move forward to early or upfront combination therapy in children with PAH. Upfront dual or triple therapy, both suggested to be effective in adult PAH, may well provide the next step in improving outcome of pediatric PAH [21,22].

If medical treatment fails, palliative Potts shunt may be considered, which was recently shown to prolong survival and improve functional capacity during longer term follow-up (median follow up 2.1 years, range 3 months–14.3 years) in drug-refractory pediatric PAH [23]. As a Potts shunt does not preclude lung transplantation, it may be considered as a surgical option before resorting to lung transplantation.

**RISK STRATIFICATION AND TREATMENT GOALS**

A goal-oriented treatment strategy is currently suggested for the treatment of pediatric PAH. However, without validated treatment goals, such goal-oriented treatment strategies cannot be established. Despite this crucial lack of data in pediatric PAH, several treatment guidelines and recommendations have been proposed for children with PAH [2,3,14,24]. In the absence of validated treatment goals, these recommendations are predominantly expert opinion instead of evidence based. An apparent lack of consensus in these opinions is demonstrated by important differences between the various reported pediatric treatment recommendations, stressing the need for evidence.

Over the last years, several studies have provided prognostic parameters that are associated with outcome and may represent disease severity. They are useful in the initial risk stratification for pediatric PAH, determining initial therapy. However, parameters with prognostic capabilities are not automatically suitable to serve as a treatment goal. Treatment goals are either clinically meaningful parameters that reflect how a patient feels or functions and can thus be a target for treatment, or should be surrogates for survival. Surrogates for survival by definition are parameters with a strong correlation with survival, which can be changed by treatment, while such change should indicate disease worsening or improvement and should be predictive of long-term outcome [25,26].

The WHO functional class (WHO-FC) was recently shown to be among the strongest prognostic predictors in pediatric PAH, according to a systematic review of literature with meta-analysis [27]. Therefore, despite the disadvantage of being a potentially subjective measurement, it has been demonstrated to be an extremely useful prognostic parameter. Furthermore, WHO-FC was shown to be a surrogate for survival and as such qualifies as treatment goal [28].

PAH leads to an increased right ventricular work load, right ventricular adaptation and eventually failure. Adequacy of right ventricular adaptation to the increased work load may be represented by coupling as a measure of right ventricular to pulmonary arterial interaction. Uncoupling may be a sign of right ventricular failure and thus predict adverse outcome. Right ventricular function can be assessed by echocardiography. In a recent pediatric PAH cohort study, it was shown that right and left ventricular dimensions, right/left ventricular dimension ratios, right atrial dimensions and right ventricular functional parameters correlate with both disease severity and outcome [29]. New echocardiographic parameters have also been suggested to be useful in pediatric PAH. Right ventricular free wall longitudinal strain determined by speckle tracking was shown to be decreased and to predict clinical worsening in children with PAH [30]. An echocardiographic method to estimate right ventricular stroke work was introduced and shown to correlate with other indices of right ventricular function [31]. So far, only tricuspid annular plane systolic excursion (TAPSE) has been shown to qualify as treatment goal [28]. Regrettably, echocardiographic variables often suffer from limited reproducibility and therefore lack of general validation. MRI measurements may be an
interesting alternative because of its better capability to provide volume measurements in the complex anatomic configuration of the right ventricular. MRI-derived measurements have been shown to be prognostic for survival in pediatric PAH [32].

At the pulmonary arterial side of ventricular-arterial coupling, pulmonary arterial stiffness parameters are gaining interest as prognostic indicators in PAH. Recently, Ploegstra et al. [33] have shown that in early pulmonary vascular disease in children, pulmonary arterial compliance and distensibility can predict the development of advanced PAH and mortality in later life. Furthermore, recently, Douwes et al. [34] showed that pulmonary arterial capacitance is related to disease severity and a predictor of prognosis in pediatric PAH, which was confirmed by Takatsuki et al. [35]. Schäfer et al. [36] used cardiac magnetic resonance techniques and found pulmonary arterial strain and arterial wall shear stress to be reduced in pediatric PAH compared to controls. In order to determine right ventricular to pulmonary arterial coupling, one should move forward to combining right ventricular and pulmonary arterial parameters to establish a coupling ratio. Recently, Truong et al. [37] have shown that a noninvasive MRI-derived measurement of ventricular-vascular coupling ratio is feasible in children with PAH. Further studies are needed to evaluate the prognostic implications of ventricular to vascular coupling parameters and their potential to be treatment goals.

The upside of serum biomarkers is that they are relatively easily obtainable measurements. They should, however, be representative for the disease process and its evolution, which is a property difficult to demonstrate. Two serum biomarkers have been repeatedly shown to have prognostic capabilities in pediatric PAH: N-terminal pro-brain natriuretic peptide (NT-proBNP) and uric acid. A recent meta-analysis confirmed that NT-proBNP correlated strongly and consistently with survival [27]. Furthermore, NT-proBNP was shown to be a surrogate for survival that qualifies to be a treatment goal [28]. Baseline uric acid levels had previously been shown to correlate with survival in pediatric PAH [38–40]. More recently, it was shown that the development of uric acid levels over time correlates with outcome in pediatric PAH [41]. These findings show that uric acid is capable of predicting outcome not only at baseline, but also during the disease course of PAH and therefore may also qualify to be a treatment goal.

Exercise intolerance may be a marker of disease severity. Very recently, it has been shown that peak systolic blood pressure during cardiopulmonary exercise testing (CPET) is associated with clinical worsening [42]. The limitation of CPET in children is demonstrated by the only randomized clinical trial performed in children with CPET as primary endpoint, in which about 50% of included patients were not able to perform CPET because of age or developmental issues [43]. Clearly, we should consider alternative methods, less dependent on children's developmental stage, to determine exercise capabilities. The 6-min walk distance has recently been shown to correlate with disease severity and predict transplant-free survival in children of 7 years or older [44]. Furthermore, accelerometry, measuring actual daily exercise activity, was shown feasible in children with PAH and accelerometer output was shown to correlate with disease severity [45]. Future studies may prove their value for guiding treatment decisions. Interestingly, a pilot-study was performed evaluating home training in pediatric PAH [46]. It is an interesting idea that training might be a therapeutic intervention that is not directed at the disease itself, but through improvement of exercise capacity might lead to an improvement of quality of life.

In 2013, Ivy et al. [2] included failure to thrive as a sign of higher risk for unfavorable outcome in their risk stratification that determines treatment initiation. This decision was based on results from the REVEAL pediatric data and the United Kingdom Service for pulmonary hypertension in Children data showing a correlation between weight and height z-scores and survival [47,48]. A specific multi-registry study on growth in pediatric PAH was published in 2016 [49]. This study showed important growth impairment in children with PAH. Height was more affected than BMI. But more importantly, height for age was associated with disease severity and duration and patients with catch up growth in height appeared to have WHO-FC improvement [49]. Therefore, growth may be a parameter that can serve as a monitor of disease severity and treatment effects. Further studies, however, are necessary to investigate whether growth is merely an indicator of outcome, or may be a specific target for nutritional or drug intervention in order to improve outcome of PAH.

**CLINICAL TRIAL ENDPOINTS**

In 2010, Haworth and Beghetti [50] described in this journal a lack of validated study endpoints for pediatric PAH. The lack of validated endpoints is one of the factors that hampers the design of pediatric trials and treatment efficacy studies [51]. Following the findings in adults with PAH, clinical worsening as a composite endpoint was recently also proposed for children with PAH, consisting of
death, lung-transplantation, nonelective PAH-related hospitalization, initiation of IV protonanoids and functional deterioration [52**]. Events of clinical worsening by this definition were shown to predict death or lung-transplantation. Furthermore, clinical worsening events were shown to occur frequently and early in the observation time. Consequently, in a clinical trial, the study time needed to reach a meaningful number of events would be reduced compared to using death and transplantation as endpoint [52**]. These results therefore suggest that time to clinical worsening is useful as endpoint for clinical trials also in pediatric PAH. The first clinical trial in pediatric PAH using time to clinical worsening as a primary outcome is about to start (NCT02932410) [53].

CONCLUSION

The lack of specific pediatric data on PAH hampered the formation of evidence-based treatment recommendations for the disease in children. However, the recent emergence of pediatric data will help the field to move forward. For the first time, evidence-based treatment goals were identified: WHO-FC, NT-proBNP and TAPSE. A composite endpoint has been introduced that will help to perform clinical trials and treatment efficacy studies in children with PAH. Future research should focus on whether the recently identified prognostic indicators may also qualify to be additional treatment goals. Moreover, the efficacy of a goal-oriented treatment strategies in pediatric PAH should be further investigated.

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REFERENCES AND RECOMMENDED READING

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