Eur Respir Rev 2009; 18: 111, 18–23
DOI: 10.1183/09059180.00011109

Paediatric pulmonary hypertension: monitoring progress and identifying unmet needs

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ABSTRACT: Recent advances in the field of pulmonary hypertension (PH) have provided clinicians with a range of treatment options, but effective disease management in children presents a unique challenge. The present article will discuss the steps being taken to address unmet needs in paediatric PH.

Understanding the epidemiology of paediatric PH is essential to guide management decisions, but such epidemiological data are scarce. The first international paediatric PH registry, Tracking Outcomes in Paediatric Pulmonary Hypertension (TOPP), promises to become a vital resource.

Studies of PH therapies are rare in children, and treatment of paediatric PH is generally guided by the adult treatment algorithm, with some adaptations. However, invasive management options, such as continuous prostacyclin infusion, even if effective, are challenging in children, and further research is required to develop appropriate treatment strategies, formulations and doses for paediatric PH. Measures of treatment success must also be defined, and the applicability of end-points from adult clinical studies remains an open question.

In summary, further epidemiological and treatment data are needed for paediatric pulmonary hypertension. The international TOPP registry will provide a valuable insight, but this must be complemented by research and development of adapted paediatric therapies. Dedicated childhood pulmonary hypertension services would optimise the diagnosis and management of this life-threatening disease.

KEYWORDS: Drug therapy, epidemiology, paediatric, pulmonary hypertension, registries, review

Historically, the prognosis of pulmonary hypertension (PH) in children has been extremely poor, but it appears to have improved markedly in recent years. This has coincided with improvements in diagnosis and general management, as well as the off-label application of adult PH-specific therapies to children [1]. However, published information concerning children with PH is relatively sparse. The present article will discuss some of the steps that are being taken to remedy unmet needs in this field, in terms of epidemiological study, development of appropriate treatment strategies and measurement of treatment success.

AETIOLOGY OF PH IN CHILDREN

Understanding the epidemiology and natural history of paediatric PH is essential to guide management decisions. Registries can provide valuable information with respect to epidemiology, diagnosis, most appropriate end-point assessments, treatment and outcomes. Whilst there are many registries of adult patients with PH, registries of children with PH are, however, less well-established and generally less well-powered. It has been possible to gain some data on PH aetiology in children from clinical trials or post-marketing surveillance studies of medical therapy, although it should be noted that these populations may be pre-selected with respect to inclusion criteria (table 1). In a two-centre clinical trial of bosentan in 86 paediatric patients with pulmonary arterial hypertension (PAH) in the USA [2], the predominant diagnoses were PAH associated with congenital heart disease (CHD; 56%) and idiopathic PAH (IPAH; 42%). A similar trend was observed in a European, prospective, internet-based, post-marketing surveillance database (table 1) [3].

There are established national registries in Switzerland, the UK and France with paediatric data published either as manuscripts or abstracts, but several other countries are currently establishing similar registries. The Swiss national registry was established in 1999 under the guidance of the Swiss Society for Pulmonary Hypertension [6]. From a national total population of ~7.5 million people, 23 paediatric patients

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Received:
December 08 2008
Accepted after revision:
December 17 2008

STATEMENT OF INTEREST
M. Beghetti has served on advisory boards for Pfizer, Actelion, Bayer-Schering, Encysive, GlaxoSmithKline, INO therapeutics, Eli Lilly and Mondobiotech. He has also received lecture fees from Actelion, Encysive and Bayer-Schering.

PROVENANCE
Publication of this peer-reviewed article was made possible by funding from Bayer Schering Pharma AG, Germany (principal Sponsor, *European Respiratory Review* issue 111).

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

TABLE 1 Aetiology of pulmonary hypertension (PH) in children

Data source	Clinical study	Post-marketing surveillance	National registry	National registry
First author [Ref.]	ROSENZWEIG [2]	BEGHETTI [3]	FASNACHT [4]	HAWORTH [5]
Enrolled patients	86	146	23	216
Females	49 (57)	71 (49)	11 (48)	117 (54)
Age yrs	0–18	2–11	0–18	0–19
PH aetiology				
IPAH	36 (42)	59 (40)	8 (35)#	60 (28)
FPAH				
PAH–mixed CTD	2 (2.3)	1 (0.7)		9 (4.2)
PAH–scleroderma		3 (2.1)		
PAH–CHD	48 (56)	66 (45)	12 (52)	104 (48)¶
PAH–other		13 (8.9)		14 (6.5)
CTEPH		1 (0.7)		
PH–pulmonary disease		2 (1.4)	3 (13)	29 (13)
PPH		1 (0.7)		

Data are presented as n, range or n (%). PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; FPAH: familial PAH; CTD: connective tissue disease; CHD: congenital heart disease; CTEPH: chronic thromboembolic PH; PPH: portopulmonary hypertension; #: includes familial PH; ¶: includes 47 patients with post-operative PH.

aged 0–18 yrs (median age at diagnosis 3 yrs) were enrolled in the registry from 1999–2005 [4]. The predominant diagnoses were again PAH associated with CHD (52%) or IPAH (or familial PAH (FPAH); 35%; table 1). New York Heart Association (NYHA) functional class II or III predominated at the first visit (17 out of 22 evaluable patients; 77.2%), and three of these patients improved from NYHA functional class III to II over a period of 2 yrs. The UK national registry was established in 2001, and analyses of treatment patterns and survival over the ensuing 5 yrs in 216 children with PAH were published recently [5]. PAH associated with CHD was the most common form of PH (48%), followed by IPAH (28%), which is consistent with previous studies. The French registry for PAH in children was established in 2005 in 21 cardio-paediatric centres that represent the majority of the large university hospitals in France [7]. Children eligible for inclusion in this registry were aged $\leqslant$18 yrs with any form of PAH, except for persistent PH of the newborn or PAH associated with CHD. All eligible subjects had to have data available from right heart catheterisation or Doppler echocardiography. Data analysis is ongoing and results have not yet been published. A national PAH registry is also currently being established in the Netherlands, but no published information is available.

The diagnostic classification of PH in children follows that adopted for adults [8], because there is no classification system that is specific for children. However, the sparse data collected to date already clearly show a different pattern of diagnoses and aetiologies for PH in children compared with adults. The predominant diagnoses in children are IPAH and PAH related to CHD, which probably account for about 90% of children with PH encountered in clinical practice. To date, very few patients with other forms of PH have been reported, but we need to know if this is due to the lack of diagnosis, lack of report or a true absence of these forms of PH in children. It is possible that PH associated with lung developmental anomalies or broncho-pulmonary dysplasia is currently underreported.

In order to address the paucity of registry data for paediatric patients with PH, the first international registry in paediatric PH was recently established: the Tracking Outcomes and Practice in Paediatric PH (TOPP) registry [9]. Up to 450 children aged $\geqslant$3 months and $\leqslant$18 yrs with previously or newly diagnosed PH (two-thirds and one-third of the registry population, respectively) confirmed by right heart catheterisation will be enrolled and followed for $\geqslant$3 yrs at 39 specialist centres in 22 countries covering four continents (Australia, Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Mexico, the Netherlands, Norway, Poland, Portugal, Switzerland, Turkey, UK and USA). The main aims of the registry are to: 1) describe the demographic and clinical characteristics of PH in children; 2) determine medical treatment and disease-management patterns in clinical practice; and 3) describe risk factors for and the clinical course of disease progression. From these data it is hoped that diagnosis and treatment guidelines will be formulated and long-term patient care will be improved.

TREATMENT OF CHILDREN WITH PAH

Treatment algorithms

There are no evidence-based treatment recommendations for children with PAH, primarily because of the lack of results from randomised clinical trials in paediatric patients. No drug therapy is approved for use in children with PAH and off-label therapy has been the pragmatic norm in this population. In practice, the therapeutic algorithm developed for PAH in adults [10, 11] appears to guide treatment of children with PAH. An adapted, simplified algorithm for the treatment of paediatric PAH has been published (fig. 1) [12].

Calcium channel blockers

Acute pulmonary vasoreactivity testing during right heart catheterisation is the initial step in determining the suitability of long-term calcium channel blocker therapy for children with severe PAH. The prevalence of acute vasoreactivity is higher in

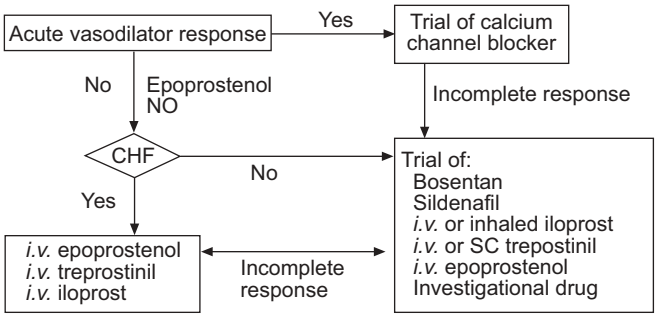

FIGURE 1. Algorithm for the treatment of paediatric pulmonary arterial hypertension. CHF: congestive heart failure; NO: nitric oxide; SC: subcutaneous. Reproduced from [12] with permission from the publisher.

children than in adults, allowing a higher proportion of children to be treated effectively with calcium channel blocker therapy [13–15]. In children with IPAH, BARST *et al.* [13] showed that 5-yr survival rates improved significantly in 31 acute vasoreactive responders treated with calcium channel blockers compared with 43 nonresponders ($p=0.0002$). Longer term follow-up revealed a 10-yr survival rate of 81% among the responders. However, careful follow-up is essential as some acute responders may become nonresponders with time and require additional treatment [16].

Intravenous prostanoids

Long-term *i.v.* epoprostenol was shown to be effective in children with IPAH in 1999 [13]. Survival was significantly improved in 31 children treated with long-term *i.v.* epoprostenol compared with 28 children in whom it was indicated but not administered ($p=0.002$). The 4-yr survival rates for treated and untreated patients were 94 and 38%, respectively. Longer term follow-up in 35 patients treated with *i.v.* epoprostenol revealed a 10-yr survival rate (including transplantation as a censoring event) of 61%, whilst 10-yr treatment success rate (defined as freedom from death, transplantation or atrial septostomy) was 37% for this group [16]. Maintenance doses of *i.v.* epoprostenol per kg of body weight appear to be higher in children than adults; titration is necessary as interindividual doses vary considerably [11]. There has been little or no published experience with *i.v.* or subcutaneous (SC) administration of other prostacyclins, such as trepostinil or iloprost, or oral beraprost in children [11]. Pain at the site of administration is frequently associated with SC trepostinil [17], and generally precludes its administration in children [11, 18].

Inhaled iloprost

Inhaled iloprost has been investigated as an alternative to parenteral prostacyclins, owing to the inherent problems associated with parenteral medication (*e.g.* requirement for an indwelling line and the associated risk of infection). Administration by inhalation also enables direct delivery of the drug to the lungs, thus reducing systemic side-effects. The effects of inhaled iloprost as add-on therapy were investigated in 22 children (median age 11.5 yrs) with PAH [19]. The majority of the children were severely ill; 10 of the children had previously had an inadequate response to PAH therapy or had refused *i.v.* prostanoid therapy, and nine of the children were switched to inhaled iloprost from *i.v.* or SC prostanoid therapy. Inhaled iloprost (median dose: 5 μg six times daily) was as effective as inhaled nitric oxide in lowering mean pulmonary artery pressure ($\bar{P}_{pa}$) and pulmonary vascular resistance index (PVRi). World Health Organization (WHO) functional class improved, remained unchanged and decreased in 35%, 50% and 15% of the children, respectively. In total, 64% of patients continued to receive long-term inhaled iloprost, with the remainder stopping iloprost because of lower airway reactivity, clinical deterioration or death. Acute bronchoconstriction was a problem in some children, as well as poor compliance with the aerosolised iloprost delivery system and requirement for frequent administration (up to nine times daily).

Bosentan

The largest cohort of children with PAH to be treated with bosentan was in an open-label, retrospective clinical trial in the USA [2]. In total, 86 patients were treated with bosentan either with or without *i.v.* epoprostenol or SC treprostinil. $\bar{P}_{pa}$ and PVRi were decreased after $\geqslant 8$ weeks of bosentan therapy. WHO functional status improved ($p<0.001$), and Kaplan–Meier survival estimates at 1 and 2 yrs were 98% and 91%, respectively, which compares favourably with historical populations [13]. Bosentan appeared to be well tolerated, with peripheral oedema being the most frequent adverse event (8% of patients). However, the results of this study need to be considered in relation to its retrospective nature and lack of a control group.

Other less well-powered, open-label studies in smaller numbers of patients, often cases series or retrospective studies, have reported on the use of bosentan in paediatric patients with PAH [20–24]. In a study specifically carried out in PAH patients with systemic-to-pulmonary shunt, bosentan therapy produced short-term improvement (4 months) with respect to WHO functional class and 6-min walking distance both in 10 children and 25 adults [25]. However, there was a progressive decline in the beneficial effect of bosentan after 1 yr. The decline was most pronounced in the children who tended to have more severe disease at baseline than adult patients.

Results from randomised clinical trials and/or long-term outcome studies are required to confirm the efficacy and safety of bosentan. The safety of bosentan therapy was recently reported from an internet-based, post-marketing surveillance database that compared 146 paediatric patients aged 2–11 yrs with 4,443 paediatric patients aged $\geqslant 12$ yrs [3]. Median bosentan exposure was 29 weeks in children. Elevated transaminase levels were reported in 2.7% of children compared with 7.8% of patients aged $\geqslant 12$ yrs, and the overall discontinuation rate from bosentan was 14% in children compared with 28% in patients aged $\geqslant 12$ yrs, suggesting that bosentan may be better tolerated in children than in adults.

An open-label, multicentre study has recently been completed which investigated the pharmacokinetics, tolerability and safety of a paediatric formulation of bosentan (a 32 mg tablet that is easily divisible into quarters) in children with IPAH or FPAH, but has not yet been published.

Sildenafil

The effects of oral sildenafil (0.25–1 $mg \cdot kg^{-1}$ four times daily) were investigated in a pilot study of 14 children aged 5.3–18 yrs with PAH [26]. Mean 6-min walk distance increased

significantly from baseline (278±114 m) to 432±156 m at 12 months (p=0.005); a plateau was reached between 6 and 12 months. Median $\bar{P}_{pa}$ and PVRi decreased significantly, and sildenafil appeared to be well tolerated. However, the results of this small study must be confirmed in a large, randomised, controlled clinical trial. Data from such a large study will become available in the very near future.

Currently no data are available for children treated with other endothelin-receptor antagonists (ambrisentan and sitaxentan), other phosphodiesterase inhibitors (tadalafil) or new therapies currently studied in adults, such as imatinib, vasoactive intestinal peptide (aviptadil) or soluble guanylate cyclase stimulators.

Nonpharmacological treatment options

Based on the current adult algorithm, surgery may be considered when the patient deteriorates despite maximal pharmacological therapy. Atrial septostomy may benefit patients with severe PAH with recurrent syncope and intractable right heart failure. Although this procedure is associated with a risk of worsening hypoxaemia, it has been shown to relieve symptoms in a case series [27]. A case study by BLANC *et al.* [28] suggested that Potts shunt (anastomosis between the descending aorta and the left pulmonary artery) may be an alternative surgical option for patients with suprasystemic pulmonary vascular resistance. Lung or heart-lung transplantation may also be offered to patients who do not respond to pharmacological therapy. The decision to refer a patient for transplantation and the timing of referral should be based on the prognosis of the patient, the local waiting time for transplantation and the expected survival after transplantation [1, 12]. The 3-yr survival rate for paediatric patients undergoing lung transplantation between July 1, 2003 and June 30, 2007 was 68.7%, according to registry data from the International Society for Heart and Lung Transplantation [29].

OUTCOME MEASURES IN PAEDIATRIC PH

There is much ongoing debate concerning appropriate end-points for the determination of prognosis and treatment response in adults with PAH [30–34]. The accepted outcome measures in clinical trials in adults, particularly standard exercise testing (6-min walk distance), functional class, haemodynamic measures (right heart catheterisation) and survival, have also been the most common outcome measures in studies of children with PAH. Given the improved survival rates in adults with PAH compared with historical cohorts, additional outcome measures (such as quality of life) [35–37] and noninvasive end-points (such as biochemical markers, *e.g.* brain natriuretic peptide (BNP) [38]) and echocardiographic or magnetic resonance imaging have attracted increasing interest [39–41].

The 6-min walk distance remains the standard tool for testing exercise capacity in most clinical trials in adults with PAH, and is an independent predictor of mortality [42]. The 6-min walk distance is difficult to standardise in children, but the recent publication of reference values in healthy children according to age (fig. 2), height and sex will assist in the future application of this end-point and its interpretation in clinical trials in children with PAH [43–45].

Right heart catheterisation in children has a clear diagnostic role, but its prognostic utility is not proven and requires validation. Children, their caregivers and their clinicians are reluctant to repeat catheterisation due to the inherent risk associated with the procedure and the requirement for anaesthesia, even when performed in expert centres [46].

In adult patients with primary PH, plasma BNP has been shown to be a noninvasive prognostic indicator [38]. A study in the UK investigated the relationship between plasma BNP level, functional status and outcome in 50 children with PAH [47], and found a positive correlation between plasma BNP level and WHO functional class. However, plasma BNP had limited sensitivity for predicting death rates or need for transplantation in this study.

A Dutch study also investigated the prognostic utility of N-terminal pro-BNP (NT-proBNP) in 29 children with PAH [48]. Higher NT-proBNP levels were associated with higher WHO functional class (r=0.34, p=0.04) and increased mortality rates (Chi-squared=9.93, p=0.002). Similarly, a prospective study in the USA of 78 children with PAH found that patients with a BNP concentration >180 pg·mL^{-1} had increased mortality rates [49]. The latter study also monitored changes in BNP levels over time and assessed their correlation with haemodynamic and echocardiographic parameters. Although absolute BNP levels did not show a strong correlation with commonly used haemodynamic and echocardiographic data, temporal changes in BNP levels correlated significantly with temporal changes in haemodynamic and echocardiographic data. Thus, monitoring of changes in BNP concentrations over time may provide a useful noninvasive means to monitor disease severity and assess prognosis in the paediatric patient with PAH.

CONCLUSIONS

National registries have been established to yield information on the diagnosis, prognosis and treatment outcome in children with PH, but patient numbers have generally been too low to provide definitive conclusions. This disadvantage should be overcome with the recent establishment of the international TOPP registry for children with PAH, which should provide extremely valuable information on medical treatment and disease management patterns, as well as the clinical course of

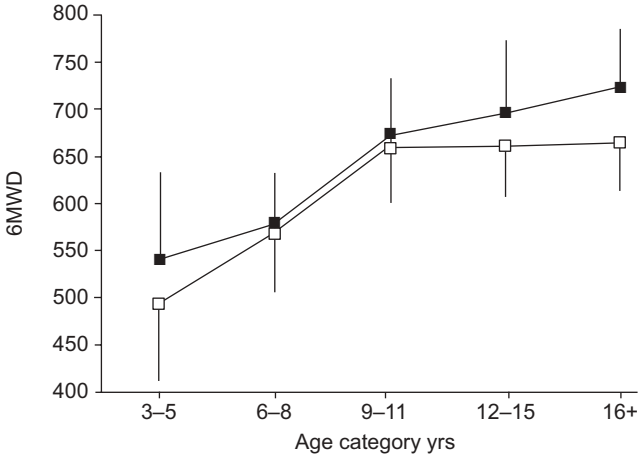

FIGURE 2. Variation of 6-min walk distance (6MWD) with age in children. □: females; ■: males. Reproduced and modified from [44] with permission from the publisher.

PH in children. The TOPP registry should assist in the development of paediatric diagnosis and treatment guidelines and in the improvement of long-term patient care.

To date, treatment of children with pulmonary arterial hypertension has been somewhat pragmatic in the absence of approved medications and has generally paralleled recommendations for adults. The recently published UK national registry indicates that survival has improved with the use of adult pulmonary arterial hypertension-specific therapies, and suggests that combination therapy (epoprostenol with bosentan or sildenafil) may achieve the best outcomes [5]. However, information concerning the treatment of pulmonary arterial hypertension in children remains scarce and there is a need for further, larger, controlled, longer term studies. Appropriate end-points, preferably noninvasive, should be identified for use in assessing treatment response. Ideally, advances in the understanding and treatment of paediatric pulmonary hypertension should be complemented by the provision of dedicated childhood pulmonary hypertension services to optimise diagnosis and management of the disease.

ACKNOWLEDGEMENTS

The author would like to thank C. Mulligan of Oxford PharmaGenesis for providing medical writing support.

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