Neonatal and Childhood Pulmonary Hypertension - An Update (2012)

Matthias Gorenflo1,*, Siegrun Mebus2, Ian Adatia3, Maria J del Cerro4, Damien Bonnet5 and Maurice Beghetti6

1Department of Ped. Cardiol and Congenital Cardiology, University Med. Ctr., Heidelberg, Germany
2Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herz Zentrum München, Technische Universität München, Munich, Germany
3Department of Pediatrics, Div Pediatric Cardiology Pulmonary Hypertension Clinic, Stollery Children’s Hospital, Mazankowski Heart Institute, University of Alberta, Edmonton, Alberta, Canada
4Pediatric Pulmonary Hypertension Unit, Pediatric Cardiology “La Paz” Hospital Madrid, Spain
5Pediatric Cardiology, University Paris Descartes, Hospital Necker, Paris, France
6Pediatric Cardiology Unit, Children’s University Hospital, Geneva, Switzerland

Abstract
Although substantial advances have been made in our understanding of pulmonary hypertensive vascular disease there remain important challenges to overcome in designing pediatric drug trials and improving long term survival. We address the current classifications and review the current knowledge on epidemiology, pathogenesis and therapy of pulmonary hypertension.

Abbreviations: 6MWT: 6-Min Walk Test; ACVRL1: Activin A Receptor Type II-Like Kinase-1; ANP: Atrial Natriuretic Peptide; APAH: Associated Pulmonary Arterial Hypertension; AVR: Acute Vasodilator Response; BMPR-II: Bone Morphogenetic Protein Type II Receptor; BNP: b-Type Natriuretic Peptide; CHD: Congenital Heart Disease; CXR: Chest X-Ray; ET-1: Endothelin-1; EPCs: Circulating Endothelial Progenitor Cells; HPAH: Heritable Pulmonary Arterial Hypertension; IPAH: Idiopathic Pulmonary Arterial Hypertension; MRI: Magnetic Resonance Imaging; PAH: Pulmonary Arterial Hypertension; PAH-CHD: Pulmonary Arterial Hypertension Associated with Congenital Heart Disease; PDE-5: Phosphodiesterase Type 5; PH: Pulmonary Hypertension; PHVD: Pulmonary Hypertensive Vascular Disease; PVR: Pulmonary Vascular Resistance; TAPSE: Tricuspid Annular Plane Systolic Excursion; TGF-β: Transforming Growth Factor – Beta; TIMPs: Endogenous Tissue Inhibitors of Matrix Metalloproteinases; TOPP: Tracking Outcome and Practice in Paediatric Pulmonary Hypertension

Introduction
Pulmonary Hypertension (PH) is a fatal disease affecting patients of all ages. In the last decade, substantial progress has been made in the understanding of the underlying pathobiology, which has been translated successfully into the development of medical treatments. This review aims to summarize our current knowledge with a special focus on pediatric pulmonary hypertension.

Definition and classification
The Dana Point classification of PH [1], (Table 1), categorizes very well the different etiologies of PH. It reflects the epidemiology of PH in adults and has been adopted by federal drug agencies to guide and monitor the use of pulmonary hypertensive specific therapy. It is an invaluable tool in the understanding of PH and facilitates drug trials in adults and has been adopted by federal drug agencies to guide and monitor the use of pulmonary hypertensive specific therapy. It is an invaluable tool in the understanding of PH and facilitates drug trials in

These problems have been discussed at a conference held in Panama in 2011. According to the Panama Classification 2011, pediatric pulmonary hypertensive vascular disease is defined as a mean pulmonary artery pressure equal or > 25 mmHg and a pulmonary vascular resistance index > 3.0 Wood units * m² for biventricular circulations [3].

The Panama classification attempts to address Pulmonary Hypertensive Vascular Disease (PHVD) more broadly than the Dana Point Classification and is particularly cognizant of the heterogeneity of pediatric PH in comparison to adult onset PH. This acknowledges the increasing awareness that post cavo-pulmonary anastomosis, exercise limitation or cyanosis may be due to an increased pulmonary vascular resistance and that these patients might benefit from targeted therapies aimed at reducing the pulmonary vascular resistance even though the mean PA pressure < 25mmHg. [4-6]. Therefore, the Panama Classification includes a definition of PHVD of PVR > 3.0 WU/m² or a transpulmonary gradient > 6 mmHg for patients after cavo-pulmonary anastomosis.

The Panama classification divides pediatric PHVD into 10 categories (Table 2) ordered according to the estimated frequency of occurrence and currently accepted pathophysiology.

Classifications are designed to adapt and respond to changes in clinical practice and knowledge of the disease. Although the Panama classification describes the pathogenesis and the pathophysiology of pediatric PHVD more fully, it is not commonly accepted yet and will likely undergo further modification in future consensus meetings such...
as the forthcoming World Symposium on Pulmonary Hypertension to be held in Nice in February 2013.

Epidemiology

Among the different issues relating to pediatric PH, the etiology and epidemiology of the disease are two of the most important. When dealing with an orphan or rare disease a comprehensive approach is to develop registries to obtain data in a large number of patients [7]. The adult community has paved the way with several registries recently published [8-15]. There are several national registries and some data are also available from large therapeutic studies and databases. These data are essential to better define the different etiologies and their importance in pediatrics. We report hereafter the current data available for pediatric PH.

Incidence and prevalence

Patients with pulmonary hypertension associated with congenital heart disease (PAH-CHD) prior to corrective surgery as well as patients presenting with (neonatal) lung disease and PAH are currently not the focus or excluded from most registries. The various and current pediatric registries have different inclusion criteria and, therefore, not only are comparisons difficult but also, may not provide a complete picture of PH in children. PAH associated with CHD represents the most preventable cause of pulmonary vascular disease worldwide [16].

If care is centralized, as in France, UK and the Netherlands, it may be possible to report incidence and prevalence of PH in pediatrics. In France, a childhood PAH prevalence of 2.2 per million has been reported [17]. In the United Kingdom, the incidence of idiopathic PAH is estimated at 0.48 per million children and the prevalence at 2.1 per million children [18]. In a large registry cohort of 3263 Dutch patients, the annual incidence and point prevalence for idiopathic PAH has been reported at 0.7 and 4.4 per million children and 2.2 and 15.6 for PAH-CHD, respectively [19]. However, and this is true for all registries, it remains impossible to be sure that a complete diagnostic workup has been performed in all patients. Notwithstanding this uncertainty, most data derive from expert centers that apply strict inclusion criteria. Therefore, it may be assumed that the data reflect the true frequency of idiopathic PAH in the pediatric population in these countries with the caveat that unless genetic testing is performed in all cases the incidence of heritable PAH will be underestimated.

Pediatric etiologies

Extensive reviews on pathogenesis of PAH including neonatal PAH are available [20]. Therefore, this review will, not focus on pathogenesis. Likewise the differences between adults and children with respect to etiology, pathogenesis and treatment of PAH have been reviewed recently [21].

The recent recognition that some kinds of pulmonary hypertensive
vascular disease may have similarities with malignant disorders, the monoclonal and polyclonal proliferation of abnormal endothelial cells in idiopathic PAH versus Eisenmengers complex suggest that there may be differences in diseases with apparently similar histology and raise the possibility that not all treatments are equally efficacious in all clinical phenotypes [22,23].

The Swiss registry included patients aged from 28 days to 18 years seen between 1999 and 2005. Out of 23 patients, idiopathic/familial was the etiology in 8 (34.8%), CHD in 12 (52.2%) and associated with pulmonary disease in 3 (13%) [24]. The treatment and survival of children with PAH referred to the UK PH service has been investigated [25]: among the 216 patients treated between 2001 and 2006, 60 had idiopathic PAH (mean age 7.4 years, 47 (62%) were female) whereas 156 had associated forms of PAH (mean age 7.9, 80 (51%) female). The authors' raised an important point, which also had been suggested by others [3], that children often have multiple contributors to PAH and, therefore, are not easily categorised within the Dana point system.

Data from the pediatric REVEAL registry, including 216 patients (mean age at diagnosis: 8.0 years) demonstrated that idiopathic PAH and associated PAH patient represented 92% (122 idiopathic, 77 CHD). Ten patients had connective tissue disease, 3 portopulmonary, 3 persistent pulmonary hypertension of the newborn and 1 another associated form [27].

The TOPP, short for Tracking Outcome and Practice in Pediatric Pulmonary Hypertension, is an international, multicenter, prospective, observational, non-interventional program set up to study the natural history of PH, focusing on diagnosis and disease management in children and adolescents in real-world clinical settings. A registry analysis from the Netherlands showed that 317 (88%) patients had PAH, which was idiopathic or familial PAH in 182 (57%), and associated with other disorders in 135 (43%), of which 115 (85%) cases were associated with CHD [28]. 42 patients (12%) had pulmonary hypertension associated with respiratory disease or hypoxaemia.
with bronchopulmonary dysplasia being the most frequent, and three patients had chronic thromboembolic pulmonary hypertension, or miscellaneous causes of pulmonary hypertension.

In summary PAH is a more heterogeneous condition in children than adults and more frequently associated with genetic syndromes. In addition PAH is more likely to be complicated by degrees of CHD and pulmonary disease, which on their own, would be unlikely to cause severe PAH.

**Genetics of pulmonary hypertension**

Pulmonary hypertensive vascular disease is associated with endothelial damage proliferation of smooth muscle cells, as well as dysfunction and resistance to apoptosis of vascular and perivascular cells. Research focusing on genetic determinants that influence proliferation has led to the discovery of heterozygous germline mutations in the gene encoding for bone morphogenetic protein type II receptor (BMPR-II) more than ten years ago [29,30]. BMPR-II is a type II receptor member of the transforming growth factor – beta (TGF-β) superfamily. The gene encoding for BMPR-II is located on chromosome 2q33. Three different BMP receptors type I and three BMP receptors type II are known. They function as serine/threonine kinases. BMPs play an important role during embryonic development especially in connective tissue (chondrogenesis) [31]. In a smaller proportion of PAH patients mutations in other genes that participate in the BMPR-II signaling pathway such as Activin A receptor type II-like kinase-1 (ACVRL1 or ALK-1), Endoglin [32] and SMAD [33] have been described (Figure I)[34]. In patients with heritable pulmonary arterial hypertension (HPAH) mutations in the BMPR-II gene have been found in 58% - 74% of patients with familial PAH [35-38]. Patients presenting with apparently sporadic PAH show BMPR-II mutations in about 10 – 40% [39]. More than 300 mutations in the BMPR-II gene have been described thus far [35,40]. The mutations have been identified in various exons of the BMPR-II gene. 30 % of mutations are missense mutations [39] leading to substitutions of highly conserved amino acids with functional impact on the ligand-binding or kinase domains. The remaining 70% of other known mutations are nonsense mutations, gene rearrangements or splice-site defects, all of them resulting in premature termination of the transcript. In female patients with HPAH, missense mutations in the BMPR-II gene are associated with earlier disease onset compared to patients with truncating mutations [41]. Mutation carriers show a variable disease penetrance, only 20% of mutation carriers develop clinical disease [42,43]. Carriers of the BMPR-II mutation often transmit the risk

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**Figure 1:** Mutations in BMPR2 and ALK-1 in the development of idiopathic pulmonary arterial hypertension. Top Diagram: In the normal vascular smooth muscle cell binding of the BMP ligand to the complex of BMPR-I and BMPR-II and subsequent phosphorylation of Smad 1, 2 and 8 modulates transcription resulting in growth arrest. Mutations BMPR-II lead to defective Smad signaling resulting in increased cell proliferation.

Bottom Diagram: In pulmonary endothelial cells mutations in both ALK-1 and endoglin finally promote loss of cell growth regulation. A mechanism which is also involved in hemorrhagic telangiectasia.
to their progeny but the majority of carriers will not develop PAH [44]. Genetic counseling of patients and/or parents must take this into account. Patients with PAH and BMPR-II mutations differ from those with IPAH without mutations and are younger at diagnosis with more severe disease as reflected by hemodynamics [40]. This may be explained by additional genetic, epigenetic or environmental factors that contribute to disease manifestation. Differential expression of the estrogen metabolizing gene CYP1B1 has been found to modify the risk for manifest PAH [45] underlining the role of additional genetic factors in pathogenesis of PAH. Despite these advances the specific critical pathway for the development of the disease is unknown. Mouse models of BMPR-II mutation offer the possibility to, not only, to elucidate disease mechanisms further, but also, to facilitate preclinical testing of new pharmacological products [46]. The role of BMPR-II in patients with APAH is unsettled: An increased frequency of BMPR2 mutations in patients with PAH-CHD has been reported [47] whereas others were unable to demonstrate such a correlation in Eisenmenger patients with atrial septal defect [48]. Associated genetic abnormalities such as somatic chromosome abnormalities have been described and indicate that a second genetic hit may contribute to the disease progression in patients with PAH and BMPR-II mutations [49].

Biomarkers of pulmonary hypertension

Proliferation and tissue remodeling are hallmarks of pulmonary vascular disease [20]. Current research focuses on biomarkers that reflect the ongoing disease process.

Atrial natriuretic peptide (ANP) and b-type natriuretic peptide (BNP) which is produced in atrial and ventricular myocardium are elevated in association with pressure overload and therefore have been found to be elevated in pulmonary artery hypertension. NT-proBNP could be superior to BNP as a survival parameter in patients with PH (different etiologies) because it may reflect both hemodynamic impairment and renal insufficiency and indicate increased likelihood of mortality [50]. Several studies in children with IPAH and APAH have shown that BNP [51] and NT-proBNP [52] correlate with functional status in children with PAH and that norepinephrine and NT-proBNP were highly predictive for mortality [52]. In children with IPAH and APAH serial measurements of BNP were found to correlate with changes in hemodynamic and echocardiographic changes in a given patient [53].

Endogenous tissue inhibitors of matrix metalloproteinases (TIMPs) control the activity of extracellular matrix (ECM)-degrading metalloproteinases (MMPs). A recent study showed that increased TIMP-4 correlated with higher class of functional impairment in adult patients with IPAH, APAH and PAH associated with thrombotic or embolic diseases (CTEPH) [54].

Circulating endothelial progenitor cells (EPCs; CD34+/KDR+ and CD34+/KDR+/CD31+/CD45-) have been found to be reduced by about 50% in patients with three forms of PAH (idiopathic/heritable, drug-induced, and connective tissue disease) [55]. Similar results were found in IPAH and Eisenmenger patients [56], while other groups have found differently characterized (CD133+) cells to be increased in the lung and circulation of PAH patients [57]. In a pilot study, an EPC capture chip has been used as a rapid bedside test for the screening and monitoring of patients with PAH [55].

Soluble biomarkers such as Endothelin-1, von Willebrand factor, metabolites of the eicosanoid pathway or measurement of circulating endothelial progenitor cells and circulating endothelial cells are of special interest [54]. Larger series analyzing the role of biomarkers in diagnosis and monitoring of patients with PAH are clearly necessary [58].

Diagnosis

The purpose of a diagnostic work-up in Pulmonary Arterial Hypertension (PAH) is to confirm the diagnosis and assess the severity of PAH by identifying the underlying conditions, evaluate pulmonary vasoreactivity and right ventricular function. Thus, consensus guidelines for screening, detecting and diagnosing PAH include a complex sequence of diagnostic tools [2,59,60]. The evidence for these guidelines was derived from studies in adults and frequently in subgroups other than PAH associated with CHD (PAH-CHD). However, in the absence of clinical guidelines focusing on pediatric PAH-CHD, these patients are currently managed with the same diagnostic paradigm as the adults, on which recently published recommendations for children are based upon [61].

PAH in children is a rare disease and in the initial stages symptoms are mild and nonspecific and diagnosis is challenging. Misinterpretation of symptoms and diagnostic findings typically delays diagnosis. Diagnosis may be delayed even when congenital heart disease is the cause of PAH. Early diagnosis is crucial as selected children with PAH-CHD may show a favorable response to targeted pulmonary hypertension drugs and may become eligible for surgical repair [62-64]. However, the "treat and repair" strategy remains to be validated, especially the long term results [65]. Early treatment of PAH may be beneficial for adolescents and adult patients [66]. Pediatric PH can present with multiple problems and may be associated with more than one underlying condition [26]. Therefore, a complete and immediate diagnostic evaluation of children with suspected PAH in a tertiary centre with expert knowledge in both -CHD and PAH- is recommended [21,61,67].

Within the last decade there has been substantial progress in diagnostic technology particularly thoracic and cardiac imaging modalities [68]. Diagnostic algorithms start with general non-invasive screening tests and lead sequentially to invasive diagnostics, specific functional tests, finally culminating in cardiac catheterization [2,61]. The indication for cardiac catheterization must be balanced in each individual patient against potential complications such as hemodynamic compromise and, therefore, should be performed only in tertiary centers familiar with the procedure with a specific team (especially anesthesiologists) with expertise.

A detailed medical history followed by a thorough physical examination are the keystones in the evaluation of a child with suspected PAH (Figure 2). Patient or parental history often reveals nonspecific symptoms such as dyspnea, syncope, recurrent upper respiratory tract infections, poor appetite and feeding difficulties with failure to thrive and in advanced stages, signs of heart failure [69]. In patients with pediatric PAH-CHD symptoms vary with the specific cardiac lesion, patients’ age, prior corrective surgery, magnitude and direction of the shunt as well as the severity of PAH [19,70].

Initial diagnostic routine screening tests include electrocardiogram (ECG) and chest x-ray (CXR). While ECG in idiopathic PAH (IPA) patients shows right ventricular hypertrophy and right axis deviation, its sensitivity and specificity are inadequate for detecting PAH particularly in pediatric CHD patients [71]. In addition, the role of Holter monitoring in the diagnostic algorithm has not been established,
although in adult CHD patients with severe PAH, rhythm disturbances are associated with a poor prognosis [56]. Although 90% of PAH patients have abnormal findings on CXR, there is little correlation with severity of PAH. A normal CXR does not allow the exclusion of PAH with certainty [72].

In PAH-CHD, imaging is pivotal to confirming the diagnosis. Echocardiography is non-invasive, provides information about structural CHD, myocardial function, and may allow estimation of intracardiac and pulmonary pressure. However it depends on adequate windows, patient cooperation and expert interpretation of findings [68]. Besides indirect cardiac signs of PAH (e.g. increased tricuspid regurgitation, right atrial and ventricular enlargement), there have been new echocardiographic measuring parameters explored within the last years such as analysis of contraction timing, myocardial tissue Doppler, Tei-Index, tricuspid annular plane systolic excursion (TAPSE), strain and strain rate. These help to recognize early right ventricular dysfunction [73,74]. Echo analysis of right ventricular morphology and function remains difficult because of the morphology and position of the right ventricle. Although data in pediatric patients are limited, cardiac magnetic resonance imaging (MRI) can provide additional information on morphology, function, and metabolism of the heart including the right ventricle [61]. Referring to this, age- and gender-matched reference values for right atrial and right ventricular hemodynamics in healthy probands have been published [75,76]. In addition, new MRI technologies offer assessment of hemodynamic parameters in the pulmonary circulation such as lung perfusion and may even replace invasive procedures in the future [59,77]. However it has to be kept in mind that MRI requires general anesthesia in many children - especially if the MR protocol requires a breath hold - which requires careful and expert anesthetic management.

The diagnosis PAH should be confirmed by cardiac catheterization to measure PA pressure, wedge or left atrial pressure and pulmonary blood flow and calculate pulmonary vascular resistance. It is recommended that cardiac catheterization and vasoreactivity testing should be performed at institutions with considerable experience in this field to minimize adverse events [74]. There are different criteria for acute vasodilator response (AVR) [78,79]. At present there is no consensus but many authorities would define a positive acute pulmonary vascular reactivity test as follows:

A) Patients without an unrestricted shunt at the ventricular or ductal level: PAPm decrease ≥ 20% and no cardiac index

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**Figure 2:** Diagnostic algorithm in children with suspected PH.
decrease (within 5% from baseline).

B) Patients with an unrestricted shunt at the ventricular or ductal level: PAPm decrease ≥ 20% and no cardiac index decrease (within 5%) or PVRI decrease ≥ 25% and no cardiac index decrease (within 5%) [78].

Results of vasoreactivity testing in patients with PAH-CHD prior to intracardiac repair are useful to decide on operability [64]. Pulmonary to systemic resistance ratios > 0.2-0.3 or PVRI > 6 – 8 Wood units *m² during acute vasodilator testing suggest an increased risk of early right ventricular failure and/or late postoperative PHVD [64,80,81].

In childhood PAH-CHD pulmonary function tests and exercise tests provide useful information during follow-up. The 6-min walk test (6MWT) is used to assess maximum exercise tolerance whereas cardiopulmonary exercise testing (CPET) should be used as a complementary test in children when the 6MWT distance is >300 m [82]. Limitations of such functional tests are patient age and validation for children with PAH. Laboratory analysis is useful to identify anemia, hemolysis, liver, or thyroid dysfunction, coagulation abnormalities, connective tissue disease and, if indicated, HIV infection.

**Medical Treatment**

Treatment guidelines for adult PAH have been published [60,72,83]. However, their evidence is based on studies in adults or children >12 years old predominantly with idiopathic/familial PAH. There are limited data for children <12 years of age. Recommendations for children with PAH-CHD are derived from therapeutic algorithms of PAH-CHD in adults.

Currently, treatment options are targeted drugs with an impact on one of three pulmonary vascular endothelial-based pathways: endothelin-1, nitric oxide, and prostacyclin pathways [84]. The primary aim of these drugs is reduction of clinical symptoms, improved quality of life and prolonged survival [85]. It remains unknown whether they modify the fundamental disease process. As there are few randomized controlled studies for drug therapy in pediatric patients with PAH-CHD, the following data are based predominantly on anecdotal reports, case series and observational reports. Notably, although there is an increasing amount of data for PAH-CHD in children showing a short-term benefit of targeted therapies, there are no long-term trials of treatment efficacy and outcome in this specific pediatric population. Moreover, except for bosentan and sildenafil, there are no targeted drugs which have been approved for the treatment of PAH in children in Europe. Before starting therapy with these drugs, careful consideration of potential benefits and risks as well as specific clinical expert knowledge with pediatric PAH should be warranted.

**Endothelin-1 (ET-1) Receptor Antagonists**

Endothelin-1 is a potent vasoconstrictor with elevated concentrations in the plasma and lung tissue of patients with PAH. There are two ET-1 receptor subtypes, ETₐ and ETₐ, mediating the activity of ET-1. Increased endothelin levels have been found inconsistently in patients with PAH-CHD [86-88]. Increased endothelin levels have been correlated to a decreased pulmonary clearance after congenital heart surgery in patients with PAH-CHD [89-91]. In addition, to date there is still no meaningful evidence demonstrating receptor selectivity as clinically relevant [92].

Bosentan is an oral non-selective endothelin receptor antagonist which is explicitly approved for the treatment of severe PAH related to congenital systemic-to-pulmonary shunts and Eisenmenger’s physiology [93]. There is a correlation between a decrease in indexed PVR and arterial ET-1 levels in response to the ETA - receptor antagonist BQ123 but at present there is no evidence for and advantage of using selective ETA - receptor antagonist compared to bosentan. In July 2009, a pediatric formulation of bosentan has become available in Europe for children with an age of at least 2 years [94].

The use of bosentan has been reported more frequently in childhood PAH than other oral PAH therapies [95]. Most of the clinical studies and observations have not differentiated between the underlying etiology of PAH within the analysis [93,96] and, therefore, no clear conclusions could be drawn for each PAH subpopulation. Moreover, the observation periods were mostly brief (weeks to months) with small case-numbers.

Available data for bosentan in infantile PAH-CHD demonstrated symptomatic improvements [97], beneficial effects in clinical status, functional class [97] and pulmonary hemodynamics after a follow-up of approximately 1 year.

However, some studies suggest that after 2 years the beneficial effects of bosentan decline more often in children than adults [99,100].

Bosentan appears to be safe and well tolerated in children and elevation transaminases is less often observed than in adults [93,97].

Among selective oral ETₐ receptor antagonists [101,102], ambrisentan has demonstrated efficacy and safety in the adult PAH population [102]. Specific data for PAH-CHD are limited in adults and children. Ambrisentan improves exercise capacity and functional class in adult PAH-CHD patients [103] but pediatric data for PAH-CHD are currently unavailable.

**Phosphodiesterase type 5 (PDE-5) inhibitors**

PDE-5 inhibitors are vasodilators with predominantly pulmonary, but also systemic effects. They are antiproliferative and inhibit platelet aggregation [104]. PDE-5 is highly expressed in the hypertrophied human right ventricle, and PDE-5 inhibition may improve myocardial contractility [105].

Currently, there are three different PDE-5 inhibitors (Sildenafil, Tadalafil and Vardenafil) which have been studied in patients with PAH. Sildenafil and Tadalafil have shown pulmonary selectivity, whereas only sildenafil improved arterial oxygenation [106]. Of note, the clinically used PDE-5 inhibitors are not exclusively selective for PDE-5 but may also inhibit PDE-1 or PDE-3, and other isoforms of the enzyme.

Current studies in pediatric PAH are limited by a short follow-up-time and overall a lack of randomized controlled studies. Pilot studies suggest efficacy and safety of sildenafil in children with PAH-CHD showing improvement in functional class, exercise capacity, and hemodynamics up to 1 year [107-108]. These benefits seem to persist for at least two years [109]. Sildenafil dosing in children is controversial. A recent study suggested that low dose sildenafil was ineffective [27]. However, another study suggested that low-dose oral sildenafil (0.5 milligrams per kilogram per day) was associated with early clinical and hemodynamic improvement up to 3 months as sufficient [110].

A recent study (STARTS-1) in 235 children (≥8 kg) showed efficacy, safety, and tolerability of oral sildenafil in children with IPAH and PAH-CHD [27]. STARTS-1 completers could enter the STARTS-2 extension [111]. In this study dose adjusted for bodyweight were used as follows:
8 kg to 20 kg: 10 mg/dose TID PO
• 20.1 to 45 kg: 20 mg/dose TID PO
• > 45 kg: 40 mg/dose TID PO.

Based on these data, sildenafil has been approved in Europe since May 2011 for children with an age of at least 1 year. The current European dosing recommendations for patients aged ≥ 1 year to 17 years are as follows:

- Patient body weight ≤ 20 kg: 10 mg/dose TID PO.
- Patient body weight > 20 kg: 20 mg/dose TID PIO.

Higher than recommended doses should not be used, until more data are available in pediatric patients with PAH because there was an increased mortality in the high dose group. Further investigation is warranted to determine optimal dosing based on age and weight. Sildenafil is finding a place in critical care settings. Oral sildenafil attenuates rebound pulmonary hypertension in children under 5 years of age with severe PH [112] and facilitated successful postoperative withdrawal from inhaled nitric oxide in children with PH following cardiac surgery [113, 114].

Intravenous sildenafil has been approved for use in adults by the FDA and EMA. Intravenous sildenafil decreased PA pressures and shortened the ICU stay in pediatric patients undergoing congenital heart surgery [115]. Higher doses of sildenafil cause systemic hypotension and if administered to patients with near normal PA pressures the intrapulmonary shunt increases and oxygenation decreases [116, 117]. Limited data in 33 children demonstrated that Tadalafil can be safely used for pediatric patients with PAH [118].

Prostacyclin and Prostacyclin Analogues

Prostacyclin is a potent pulmonary and systemic vasodilator with antiplatelet activity, and appears to have inotropic effects, endothelial cell stabilization and antiproliferative effects when used long-term [119]. Prostacyclin and longer acting analogues are administered by continuous infusion intravenously or subcutaneously [120] or by intermittent inhalation. Intravenous epoprostenol has been demonstrated to improve outcomes in children with IPAH and PAH-CHD [121]. Inhaled iloprost has the advantage of a longer half-life [119] and may require fewer inhalations. However, it is often not possible to achieve high enough doses with intermittent inhalation in severely ill children [122, 123]. Subcutaneous Treprostinil has been used as rescue therapy for in children with refractory pulmonary arterial hypertension in a small series [126].

Combination therapy

For symptomatic patients who failed to improve with monotherapy, combination therapy may exert synergistic effects through targeting different molecular pathways [124]. Unfortunately, randomized-controlled trials in children with PAH-CHD are lacking, although in clinical settings more and more children receive combination therapies [84], perhaps supporting general effectiveness, safety and tolerability [125].

In adults, recently one randomized, placebo-controlled, double-blinded trial with combination therapy of bosentan and sildenafil in Eisenmenger patients (n = 21) has been published. After a relative short period of 3 months, treatment with bosentan significantly improved walking distance and pulmonary hemodynamics, while adding sildenafil to bosentan did not cause significant effects [126]. Sildenafil and bosentan may affect blood levels of each drug and dose adjustments may be required during combination therapy [127].

The optimal timing of combination therapy remains unclear. The financial implications of expensive combination therapy need careful consideration.

Investigational Therapies

Even though available pulmonary vasodilatory drugs showed beneficial effects in pediatric PAH by improving symptoms, PAH remains a fatal disorder [128]. Alternative approaches undergoing evaluation at present include:

- New substances that address specific receptors mediating pulmonary vasodilation such as the selective prostacyclin receptor (IP receptor): Selexipag an oral, selective IP receptor agonist has been studied in a Phase II proof-of-concept study [129].
- Direct stimulators of soluble guanylate cyclase (sGC) such as Riociguat (BAY 63-2521) are under investigation [130]. Direct stimulation of soluble guanylate cyclase (sGC) has the potential (yet theoretical) advantage of being independent of endogenous nitric oxide synthesis.
- Newer agents with novel targets such as cell proliferation, inflammatory and immune pathways [20, 85, 131] may have the potential to reverse pulmonary vascular remodelling, restore the endothelial function and to reverse PAH [85].
- There have been encouraging results in preclinical animal models and application to human disease is being considered [20, 125, 131-133].

Follow-up of children with PAH

Follow-up of children with PAH remains challenging as the available tools used in the adult population are either not suitable for small children or have not been evaluated for children in this condition. The aim of the follow-up is to organize a regular evaluation of children with PAH with focus on variables with prognostic importance, i.e. variables that assess disease severity, stability and indicate prognosis. Indeed, follow-up and patient status assessment will rely on information derived from a panel of tests including clinical evaluation, exercise tests, biochemical markers, and echocardiographic and hemodynamic assessments [60, 134]. Limited data are available on this panel of markers in pediatric PAH. Heart rate recovery at one minute of rest (HRR1) after 6-minute walk test is a strong predictor of clinical worsening in adult patients with IPAH [135].

As indicated in the currently available guidelines, the clinical condition of a child can be defined as stable and satisfactory, stable but not satisfactory, unstable and deteriorating. In clinical practice, clinical deterioration is easy to identify when right ventricular failure or syncope are apparent. Conversely, assessing exercise performance by the 6MWT or by cardiopulmonary exercise testing has many limitations related to age and availability [136]. Echocardiographic parameters that reflect right ventricular function such as TAPSE and the presence of pericardial effusion may be useful but the prognostic significance has not evaluated in children. Normal values for TAPSE in children, with age specific percentiles, are available [137]. Exploratory studies are ongoing to determine whether combination of functional and morphological RV parameters might be useful to collect. Finally, repeat cardiac catheterization to obtain hemodynamic measurements in cases with an uncertain response to therapy is important if additional...
therapy is available. Routine right heart catheterization to confirm improvement with treatment is more debatable. As in adults, it is of utmost importance that children with PAH are regularly followed in a pediatric PAH referral center that have facilities, skills and a sufficient volume of patients to obtain the best outcomes.

Despite the use of a panel of relevant biomarkers, it is difficult to predict the time to clinical worsening in pediatric PAH. Indeed, treating children according to the concept of “goal-oriented” treatment or “treat to target” is limited by the availability and validation of the currently used biomarkers. Whether or not this strategy is applicable to infants and children with PAH remains unclear. Defining age-adapted composite endpoints of therapy that may predict clinical worsening would be of great help. Recently published data on survival in pediatric PAH in the current era of targeted PAH treatments demonstrated improvement of survival with PAH therapies compared to predicted survival based on historical cohorts [25]. Data from the Dutch registry reveals that, since the introduction of second-generation drugs, only selected children demonstrated improved survival [138]. These findings suggest that current therapy remains suboptimal and that earlier more aggressive use of combination therapy, based on a composite of clinical endpoints and biomarkers to assess response to therapy are needed to recognize insufficient improvement and to predict future deterioration.

Summary

Neonatal and childhood pulmonary hypertension vascular disease presents unique challenges in diagnosis, classification, functional assessment and drug trials. Recent epidemiological studies are beginning to highlight the differences between childhood and adult disease. There are unique symptom complexes and disease phenotypes which require a comprehensive classification system to improve diagnosis and to understand the effect of therapies in different age and diagnostic groups. Age and developmentally appropriate outcome measures and biomarkers require further investigation so that we avoid missing important therapeutic effects not apparent in children too young to undertake for instance a 6 minute walk or too sick to undergo cardiac catheterization. The prenatal origins of pulmonary vascular disease and importance of vascular hypoplasia and maldevelopment form an important but under investigated aspect of the phenotype and disease progression in childhood. Nevertheless the availability of 5 different classes of drugs with which to treat children with PH is a remarkable advance over the last 30 years. Given that most referral centers will see relatively few patients with PHVD, imaginative and collaborative approaches to drug evaluation in children will be required in the future. Currently combination therapy and the impact on pathological signaling pathways may offer the best hope of improving quality of life and survival. Reversal of the abnormal endothelial cell and smooth muscle interface remains elusive.

Although substantial advances have been made in our understanding of pulmonary hypertension vascular disease there remain important challenges to overcome in designing pediatric drug trials and to improve long term survival.

Funding

This work was not funded by any grant. There were no fees or support of industry to any of the authors for writing this manuscript.

References


