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Progress in the Diagnosis and Management of Pulmonary Hypertension in Children

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Abstract

Purpose of Review—Pulmonary hypertension (PH) is a complex disease that extends beyond merely elevated pulmonary blood pressures and right ventricular dysfunction. Its multiple etiologies and ever-expanding diagnostic tools and therapeutic approaches make it a heterogeneous disease with widely variable clinical sequelae. There are still many unanswered questions that challenge our understanding of this disease.

Recent Findings—The study of PH in the pediatric patient is as robust as ever, with the creation and inclusion of pediatric-specific disease characteristics in the most recent World Health Organization classification system, improved understanding of the pathophysiology of PH in pediatric diseases like bronchopulmonary dysplasia, and increasingly expanding diagnostic tools and management possibilities. While the use of PH therapies in children previously often relied on expert opinion and inferences from studies involving adults, pediatric-targeted research is becoming more widely supported and pursued, and even has come under recent debate, which at the very least stimulates further collaboration and discussion.

Summary—This review will highlight the changes in the PH classification system, briefly explore PH in bronchopulmonary dysplasia, and provide updates on the diagnostic and management tools used by experts in the field.

Keywords

pulmonary hypertension; bronchopulmonary dysplasia; pediatrics; diagnosis; treatment

Introduction

Pulmonary hypertension (PH) continues to be a significant contributor to morbidity and mortality in pediatric patients. Its broad spectrum of pathogenesis, disease manifestation, therapeutic approach, and prognosis makes it a challenging, yet rewarding, area of medicine.

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The inclusion of the following papers with annotations is important for the following reasons: 15 – Bhat 2012 – One of initial key studies *prospectively* evaluating PH in patients with BPD and identifying the need to repeat echocardiography beyond 4-6 weeks of life. Given relatively substantial discussion of BPD in our paper, we feel that highlighting the study is important. 49 – Barst 2012 – Landmark study of sildenafil in pediatric patients that led to the controversial FDA warning placed on this drug, a staple of PAH treatment in pediatric patients. Significant discussion is devoted to this topic and highlighting this paper is essential.

From fetus to adolescent, child to adult, PH can involve or result from genetic, cellular, and physiologic derangements of the pulmonary, cardiovascular, hepatic, hematologic, and connective tissue systems. In children, prematurity, congenital heart disease, and other diseases like bronchopulmonary dysplasia (BPD) play a particularly important role in lung development and integrity. Regardless of the cause, PH and pulmonary arterial hypertension (PAH), which more specifically defines abnormalities of the pre-capillary pulmonary vasculature, share at their core the untoward effects of elevated pulmonary pressures on right ventricular size, function, and overall health and mortality. This review will discuss recent advances in our understanding and management of pediatric pulmonary hypertension.

Updates on the Clinical Classification of Pulmonary Hypertension

To systematically and appropriately apply what we learn in PH, a diagnostic classification has been developed and modified at the World Symposiums on Pulmonary Hypertension (WSPH). Initially developed at the second WSPH in Evian (France) in 1998 and subsequently updated in 2003 at the third WSPH in Venice (Italy) [1], this clinical classification system identifies five categories of disorders that cause PH, with each group sharing similar hemodynamic, pathologic, and management features; PAH (Group 1); PH due to left heart disease (Group 2); PH due to chronic lung disease and/or hypoxia (Group 3); chronic thromboembolic PH (Group 4); and PH due to multifactorial mechanisms (Group 5).

The last significant changes to this classification system came at the fourth WSPH in Dana Point (USA) in 2008 [2] and have since been widely accepted in clinical and regulatory realms. It was not until the most recent fifth symposium in Nice (France) in 2013, however, that additional pediatric-specific categories of PH were added and previous ones, expanded, resulting in a new classification system that for the first time encompasses PH patients of all ages [3**]. A separate pediatric classification system was discussed in Nice, but the 5th WSPH Task Force on Pediatric PH ultimately decided that children and adolescents should retain the same PH classification when they transition from pediatric to adult care. The expanded classification system [Table 1] now includes independent categories of persistent pulmonary hypertension of the newborn (PPHN), which is a separate category due to its unique pathobiology and greater likelihood to resolve, congenital/acquired left heart inflow/outflow tract obstruction, such as supralvalvar mitral ring, cor triatriatum, and left ventricular outflow obstruction, and congenital cardiomyopathies (a new sub-type of Group 2). These, coupled with previous categories of PAH due to congenital heart disease, PH due to developmental lung diseases, and PH due to chronic hemolytic anemia such as sickle cell disease (SCD), better represent the spectrum of PH in children and adolescents. Of note, SCD and other chronic hemolytic anemias were moved to Group 5 given their disparate pathology, hemodynamics (including possibility of left ventricular diastolic dysfunction), and response to therapy. Finally, segmental PH, which incorporates patients with pulmonary atresia with ventricular septal defect, was added as a sub-type of Group 5 disease. The 5th WSPH went on to emphasize the lifelong nature of PAH associated with congenital heart disease and also expanded its section on heritable PAH as new culprit gene mutations have been discovered in SMAD9 [4], caveolin-1 [5], and potassium channel KCNK3 [6*].

Pathophysiology

The pathophysiology of pulmonary vascular disease resulting in PH has routinely centered around pulmonary arteriopathy characterized by endothelial smooth muscle dysfunction, intimal thickening, and medial hypertrophy, with increased production of proliferative factors and decreased function of vasodilatory mediators [7,8]. Children and adolescents often have idiopathic PAH (IPAH) or congenital heart disease (CHD-PAH) [9-12] and in these cases this pathophysiology applies. Of additional importance in the pediatric population, however, is altered lung development and integrity, as is manifested in bronchopulmonary dysplasia (BPD), the most common chronic lung disease in children. This disease carries significant morbidity and mortality, especially when pulmonary pressures are elevated, and its impact on pediatric PH is substantial and worth further discussion.

The incidence of BPD has widely varied within the literature, but may be as high as 18% in infants weighing <1,500g [*13]. In infants with BPD, PH can occur in ~18-25% [13*, 14,15*]. In a recent, large, prospective, single-center study, 145 extremely low-birth-weight infants (birth weight less than 1000g) underwent screening echocardiography at a median age of 31 days of life and 6% (9/145) were found to have PH, with an additional 12% (17/145) developing signs of PH on subsequent echocardiograms, with a median age of diagnosis of 112 days of life [15*]. These studies have consistently shown that infants with more severe BPD are at greater risk of developing PH and have longer hospitalization times and higher mortality [Figure 1]. The mortality can be significant, with another retrospective study of patients with BPD and PH showing mortality rates as high as 36% at 6 months, 39% at 1 year, and 48% at 2 years after the diagnosis of PH [17]. While this study pre-dated PH-specific management therapies in BPD care, it highlights the significance of this disease in already vulnerable, premature infants.

Exploring BPD's pathophysiology has informed our understanding of pulmonary vascular biology in PH as was nicely described in a 2013 Current Opinion in Pediatrics review by Mourani and Abman [16**]. Briefly, impaired vascular growth and signaling, coupled with hypertensive vasculopathy and remodeling that occurs in the setting of lung and heart disease and chronic hypoxemia, provides the perfect substrate for the development of PH [16**]. The same group expanded its discussion of PH pathogenesis and management in an extensive review just recently published [18**].

Diagnosis

Echocardiography continues to be the most reliable non-invasive screening tool in patients with risk factors or symptoms of PH [19**]. With a reliable tricuspid regurgitant jet velocity, one can calculate an estimated right ventricular systolic pressure that, in the absence of right ventricular outflow obstruction, approximates systolic pulmonary artery pressure. This remains an important tool for the diagnosis and surveillance of PH and carries a sensitivity of ~89% [20*]. However, some patients with severe PH may have only trivial tricuspid regurgitation or poor imaging windows resulting in an incomplete Doppler pattern and underestimation of PH. Systolic interventricular septal flattening [21*], right ventricular and atrial enlargement, right ventricular hypertrophy or systolic dysfunction, and reversal of

intracardiac shunt direction (if present) are other commonly known echocardiographic signs of PH and can help in the overall assessment of this disease. Other echocardiography-based markers, like the ratio of systolic to diastolic time [22], end-systolic right ventricular to left ventricular diameter ratio [23*], tricuspid plane annular excursion and eccentricity index [21*,24**], and tissue Doppler indices [24**,25,26] have additionally been studied in recent years and may prove to be helpful going forward.

Non-invasive diagnosis and surveillance of PH now goes beyond the echocardiography lab and into the magnetic resonance imaging suite, where reliable anatomical and functional assessments of the right ventricle and pulmonary arteries can be performed. Although a challenging test in young patients with severe PH who are at high risk of problems with sedation, cardiac magnetic resonance (CMR) is increasingly becoming faster and more readily available. A recent study of 100 pediatric patients evaluated the prognostic capability of CMR in the assessment of PH and found that measurements of right ventricular ejection fraction and left ventricular stroke volume index were most strongly predictive of survival [27**]. Others have looked at wall shear stress in pulmonary arteries by phase contrast imaging in CMR and identified that it is decreased in patients with PAH relative to controls due to greater pulmonary artery dilatation with preserved systolic flow. This abnormal shear stress is believed to affect cellular mechanics, with altered inflammatory cytokine expression in more distal vessels, resulting in the medial hypertrophy and vascular pathology seen in PH [28*].

In those patients with suspected PH by echocardiography or CMR, right heart catheterization remains the definitive test to confirm PH (mean pulmonary artery pressure, mPAP, >25 mmHg), identify PAH (PH plus a pulmonary capillary wedge pressure, PCWP, <15 mmHg and pulmonary vascular resistance, PVR, >3 Wood units), and perform acute vasoreactivity testing (AVT) with nitric oxide to guide management. AVT is routinely performed in patients with idiopathic PAH or heritable PAH, and translating this practice to those with PAH due to congenital heart disease is often done as well. In children, calcium channel blockade (CCB) can be used as initial therapy in those who have a 'positive response' to AVT with nitric oxide, as defined by a decrease in mPAP $\geq 20\%$ with a cardiac index that increases or remains unchanged and a ratio of pulmonary to systemic vascular resistance that decreases or remains unchanged [29]. In adults, a decrease in mPAP and PVR $\geq 20\%$ [30] or a decrease in the mPAP by 10 mmHg to a value <40 mmHg with no decrease in cardiac output [31], define a positive response to AVT. The timing of changing a patient's management from the pediatric to adult definition of a positive response to AVT is unknown but is likely in mid-adolescence. Additional hemodynamic parameters that are prognostic in PH include the ratio of mPAP to mean systemic artery pressure, PVR to systemic vascular resistance, elevated right atrial pressure (primarily in adults), and indexed PVR >20 Wood units $\times m^2$ [32**,33, 34], and the *persistence* of positive vasoreactivity testing, the latter of which has been shown to correlate with improved survival [11]. Recently, right ventricular stroke work (RVSW), or the product of mPAP and stroke volume and an assessment integrating contractility, afterload, and ventriculo-arterial coupling, has been shown to correlate with disease severity [35*]. At the 5th WSPH, the Task Force on Diagnosis and

Assessment nicely discussed the challenging questions surrounding hemodynamic definitions of PH and PAH [19**].

The six-minute walk distance and cardiopulmonary exercise test (CPET) remain less invasive and relatively inexpensive ways to follow patients between cardiac catheterizations and CMRs. Although less validated in the pediatric population, these tests can be reliably performed and are most helpful as a surveillance tool for an individual patient. Within the CPET, evaluation of markers other than peak VO₂, such as the ventilatory efficiency slope (VE/VCO₂ slope), have also been shown to correlate with functional capacity, disease severity, and outcomes [36*]. These tests have correlated with the World Health Organization (WHO) functional class assessment, which has been shown to contribute to a risk equation for PAH worsening and survival [37]. Often, simply identifying the patient's functional class goes a long way at helping with prognosis and management. A pediatric-specific functional class has been proposed, but not yet validated [38].

Finally, our diagnostic and surveillance capabilities are improving through the measurement of serum biomarkers such as brain natriuretic peptide (BNP) or the inactive N-terminal cleavage product of its pro-hormone (NT-proBNP) which, when elevated, have been associated with greater risk of death [39-43]. Additionally helpful is our growing ability to identify specific gene mutations such as those described previously. The genetic and epigenetic evaluation of patients with PH will increasingly become a part of our diagnostic and therapeutic approach to this disease and often informs our understanding of pathophysiology, as has been told in the story of bone morphogenetic protein receptor 2 (BMPR2). Mutations in this gene have been involved in multiple signaling pathways implicated in the development of PH. Our current understanding of BMPR2 regulation suggests that although 80% of familial PH is caused by a BMPR2 mutation, almost all forms of PH share abnormal BMPR2 signaling [44**].

Management

Inherent in studying any complex and rare pediatric disease is the lack of large clinical trials in children and the need to extrapolate data from adult studies or experiences. This is particularly the case in PH management given the breadth of disease phenotype and severity, coupled with an increasingly growing list of possible therapies, many with significant adverse effects.

At the fifth WSPH in Nice, a pediatric-specific treatment algorithm was proposed using expert opinion, and although most applicable to children with idiopathic PAH, is worth reviewing further [Figure 2]. Basic therapies such as diuretics, oxygen, anticoagulation, and digoxin should be used on an individual basis and are often started during the diagnostic evaluation of a newly symptomatic patient. Right heart catheterization is routinely performed and should include AVT, with the initiation of CCB only in children with a positive AVT response, as described previously. For those with a negative response to AVT or failure to improve with CCB, risk stratification should guide initial therapeutic choices. Severe right ventricular enlargement or dysfunction, pericardial effusion, significantly elevated or rising BNP or NT-proBNP, progression of symptoms, clinical evidence of right ventricular failure, poor functional class (WHO class III, symptoms with most activities, or

WHO class IV, symptoms at rest), and syncope all suggest higher risk [TABLE 2], for which early combination therapy or IV therapy should be initiated [32**]. In those without these risk factors, single-agent oral therapy should be followed later by combination therapy if needed. Important in any of this management is frequent reassessment of these parameters and willingness to adjust therapies before right ventricular dysfunction or right heart failure ensues.

Initial single agent oral therapy should include either an endothelin receptor antagonist such as bosentan [45], ambrisentan [46], or macitentan [47*], the latter having been recently approved by the Food and Drug Administration (FDA). Perhaps more commonly started is a phosphodiesterase-5 inhibitor (PDE-5i) such as tadalafil [48] or sildenafil [49**]. Sildenafil came under particular scrutiny by the FDA during the summer of 2012 due to a (barely) clinically insignificant improvement in the pre-specified primary outcome, peak VO₂ ($p = 0.056$), in the total aggregate of low- (10mg), medium- (10 to 40mg), and high-dose (20 to 80mg) administrations of sildenafil in the STARTS-1 trial [49**], coupled with an increased risk of mortality in the high-dose group with chronic use, who not surprisingly happened to have worse baseline hemodynamics before drug administration [50**]. In August 2012, the FDA went on to place a drug warning on (chronic) sildenafil use in children (ages 1 to 17 years) [51], inciting a collective gasp from parents of children on this medication and providers who had been prescribing it for years. Some providers interpreted this warning as a contraindication to administer the drug to children and stopped prescribing it altogether, so the FDA later went on to clarify their stance in March 2014, stating that “this (initial) recommendation was NOT intended to suggest that Revatio should *never* be used in children” [52**]. On further evaluation of these studies and recent review of pediatric PH registries, many PH providers are in agreement that low-dose sildenafil has a role in the management of this disease and that high-dose sildenafil should be avoided [53*,54*,55*]. Importantly, PDE-5i therapy should not be abruptly stopped as PH worsening and mortality may increase [54*].

In children who fail single-agent oral therapy or who have substantial risk factors for severe PH, combination therapy (early or add-on) or initiation of inhaled, subcutaneous, or intravenous prostacyclins may improve survival [FIGURE 3]. Inhaled prostacyclins (iloprost and treprostinil) have been shown to be a benefit as add-on therapy in low-risk patients [57,58] or as a diagnostic tool in AVT [59]. High-risk patients warrant initiation of intravenous epoprostenol or treprostinil [59,60]. Subcutaneous prostacyclin therapy is additionally carrying momentum [61]. Finally, those high-risk patients who are still declining despite prostanoids deserve consideration for atrial septostomy [62] or lung transplantation [63]. A descending aorta to left pulmonary artery shunt has been advocated by some groups [64] and may even be placed transcatheterously, but experience is limited [65].

Newer therapeutic agents and novel approaches include the recently FDA-approved soluble guanylate cyclase stimulator, riociguat, which increases cGMP production and vasodilation independent of the nitric oxide pathway [66]. This medication has been approved for adults with WHO Group 1 PAH and patients with chronic thromboembolic pulmonary hypertension (CTEPH) who are not candidates for pulmonary endarterectomy or who have

failed this therapy [67*]. Riociguat causes bone dysplasia and growth plate injury in young, growing rats raising questions as to its use in pediatric patients [68]. Additionally, oral treprostinil was recently FDA-approved and is now commercially available [69*,70*]. As newer oral agents continue to emerge, the risks of chronic intravenous or subcutaneous prostanoid infusion may be avoided in some patients. Despite these advances, physicians remain challenged by the lack of evidence in deciding on drug therapy in children with PH.

Conclusion

Much of what we know about PH in children and adolescents, including our understanding of its pathogenesis and therapy, continues to be largely extrapolated from adult patients and studies. While collaboration between centers and within multi-disciplinary teams is certainly improving, much is still to be known about the unique aspects of PH in pediatric patients. Advancing our diagnostic and therapeutic understanding of PH comes through review of the recent literature, but additionally important is our development of patient registries as well as the ongoing participation of patients and providers in national and international organizations devoted to PH research. It is through this collective approach to this disease that we will continue to improve care of these complex patients.

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Key Points

- The WHO classification of pulmonary hypertension (PH) was amended in 2013 and now includes improved identification of pediatric-specific characteristics of the disease.
- The presence of PH increases morbidity and mortality in patients with bronchopulmonary dysplasia and relates to impaired vascular growth and signaling, coupled with hypertensive vasculopathy and remodeling stimulated by chronic hypoxemia.
- While echocardiography and cardiac catheterization remain key diagnostic tools in PH, novel uses of magnetic resonance imaging and new targets in the areas of exercise physiology, biomarkers, and genetics are enhancing our diagnostic and prognostic abilities.
- Although 80% of familial pulmonary arterial hypertension (PAH) is caused by mutations of the bone morphogenetic protein receptor 2 (BMPR2), almost all forms of PH share abnormal BMPR2 signaling.
- Within the past year, three new drugs were approved by the FDA to treat PAH in adults and will encourage ongoing discussion about use in children. Additionally, the chronic use of sildenafil in pediatric patients came under scrutiny but continues to be a mainstay of therapy at lower doses.

Figure 1.

Incidence of Pulmonary Hypertension According to Severity of Bronchopulmonary Dysplasia Severity

Incidence of pulmonary hypertension increases with severity of bronchopulmonary dysplasia, as described in two recent studies. Reprinted with permission, Mourani, et al. *Curr Opin Pediatr* 2013; 25:329-337 [16**].

Figure 2.**Proposed Treatment Algorithm for Idiopathic Pulmonary Arterial Hypertension**

Treatment algorithm proposed in the management of pediatric patients with idiopathic or heritable pulmonary arterial hypertension. May be translatable to other patients with pulmonary hypertension. CCB = calcium channel blocker; ERA = endothelin receptor antagonist; PDE-5i = phosphodiesterase 5 inhibitor. Reprinted with permission, Ivy, et al. J Am Coll Cardiol 2013;62:D117-26 [32**].

Figure 3.

Survival According to Extent of Pulmonary Hypertension Therapy

Survival improves on combination therapy for pulmonary hypertension over mono- therapy.

CCB = calcium channel blocker. Adapted with permission, Zijlstra et al. J Am Coll Cardiol 2014; in press [56**].

Table 1

2013 Updated Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2 Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanism

- 5.1. Hematologic disorders; myeloproliferative disorders, splenectomy
- 5.2. Systemic disorders: sarcoidosis, pulmonary Langorhans cell histiocytosis: lymphangiomyomatosis, neurofibromatosis, vasculitis
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 2.4. Others; tumoral obstruction, fibrosing mediastinals, chronic renal failure on dialysis

Current classification system of pulmonary hypertension, updated at the 5th World Symposium on Pulmonary Hypertension, with most recent changes highlighted in bold. ALK1 = activin A receptor type II-like kinase-1, also called ACVRL1; BMPR2 = bone morphogenetic protein receptor 2. Reprinted with permission, Simonneau, et al. *J Am Coll Cardiol* 2013; 62:D34-41 [3**].

Table 2

Risk Factors in Pediatric Pulmonary Hypertension

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
I,"	Growth	Failure to thrive
	WHO functional class	III,IV
Minimally elevated	SBIMP/NTproBNP	Significantly elevated Rising level
	Echocardiography	Severe RV enlargement/dysfunction Pericardial Effusion
Systemic CI >3.0 l/min/m ²		
mPAP/mSAP <0.75	Hemodynamics	Systemic CI <2.5 l/min/m ²
Acute vasoreactivity		mPAP/mSAP >0.75
		RAP >10 mm Hg
		PVRI >20 WU·m ²

Risk factors that should be considered when planning therapeutic management options in pulmonary hypertension. CI = cardiac index; mPAP = mean pulmonary artery pressure; mSAP = mean systemic aortic pressure; NT-proBNP = N-terminal-proBNP; PVRI = indexed pulmonary vascular resistance; RAP = right atrial pressure; SBNP = serum brain natriuretic peptide. Reprinted with permission, Ivy, et al. J Am Coll Cardiol 2013; 62:D117-26 [32**].