Idiopathic and Heritable Pulmonary Hypertension in Children: New Insights into Causes, Evaluation, and Treatment

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Over the past decade, major progress has occurred in the care of children and adults with pulmonary arterial hypertension (PAH). Recent insights into molecular mechanisms implicated in the development of pulmonary vascular disease have led to revised clinical classification and diagnostic strategies.[1] Data from multicenter pulmonary hypertension registries have provided increased understanding of the clinical course and natural history of many subtypes of disease.[2-4] Additionally, the development of multiple therapies targeting important pathways of disease and the translation of those treatments to pediatrics have led to improved life experience and survival for many children with PAH.[5]

CLASSIFICATION

Although etiologies of pulmonary arterial hypertension (PAH) in children may differ from those in adults, idiopathic and heritable forms of pulmonary arterial hypertension (IPAH/HPAH) constitute a significant percentage of all cases and pose distinctive diagnostic and treatment challenges. Primary pulmonary hypertension (PH) was reclassified as idiopathic or familial at the World Health Organization (WHO) symposium in 2003,[6] and this was revised at Dana Point (2008) to reflect current understanding of inherited PH.[1] Idiopathic PAH refers to disease without other recognized cause in an individual without family history of PH. Heritable PAH is diagnosed in those patients with 2 or more family members with disease as well as those without family history found to have genetic mutations associated with PAH.[7] Initially identified by linkage analysis in families with PAH,[8,9] mutations of a receptor member of the transforming growth factor-β (TGF-β) superfamily, bone morphogenetic protein receptor type 2 (BMPR2), are found in more than 70% of patients with familial PAH[10,11] and 25%[12] of patients with IPAH. The TGF-β superfamily consists of cell surface receptors and signal transduction factors which play critical roles in cell proliferation and growth. Mutations in other TGF-β family receptors, activin-like kinase-type 1 (ALK1) and endoglin (ENG), have also been implicated in PAH associated with hereditary hemorrhagic telangiectasis (HHT).[13,14] Heritable PAH is therefore subdivided into groups with BMPR2 mutations, those with ALK1 or ENG mutations with or without HHT, and unknown, a group reflecting approximately 30% of patients with familial disease without one of the above mutations.

PREVALENCE

Idiopathic PAH is, by definition, a diagnosis of exclusion and can only be made once other secondary contributors to PAH have been considered and deemed not involved in pathogenesis. Hereditary cases of PAH may be suggested by family history, the presence of HHT, or genetic testing. Etiologies of PAH in children are different from those in adults; however, national registry data and retrospective cohort studies from single academic institutions have collectively suggested that idiopathic and hereditary PAH comprise approximately 30% to 40% of pediatric cases of PAH.[15] The true incidence of HPAH, in particular, is unclear as uniform standards for genetic evaluation have not been utilized in widespread clinical practice. Additionally, family history may be an unreliable surrogate for diagnosis of HPAH as details of the family history may be incomplete, family members may have syndromes with incomplete clinical penetrance, and patients may present with de novo mutations as incident cases.

GENETICS

The known genetic causes of PAH are autosomal dominant and have variable penetrance; only 20% of persons with a BMPR2 mutation are likely to develop clinically significant PAH.[9] Age at development of symptoms varies, and it appears likely that there are additional genetic or modifying factors involved in the pathogenesis of disease.[16-18] A 2.5:1 female predominance[2] is recognized in both IPAH and HPAH, and estrogen mediating effects are theorized. There is recent evidence for genotype-phenotype correlations with altered disease severity associated with truncating vs missence BMPR2 mutations.[19]

The availability of genetic analysis has allowed for increased recognition of HPAH in pediatric age groups. Clinical reports suggest that successive generations present with PH symptoms at earlier ages (genetic anticipation), but the mechanism for this is not clear.[20] Mutation analysis of a group of 16 children with idiopathic PH presenting under the age of 6 found TGF-β receptor mutations in 25% (BMPR2 [2], ALK1 [1], ENG [1]).[21] Evaluation of a larger series of 78 children with IPAH/familial PAH found BMPR2 mutations in 8 (10%).[22]

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Specialized clinical features are associated with HPAH in patients with HHT. Displaying autosomal dominant inheritance, HHT is associated with mucocutaneous telangiectasias, recurrent epistaxis, and large vessel arteriovenous malformations (AVM), particularly in the lung, liver, and brain. Large vessel pulmonary AVMs may be associated with hemodynamically significant right to left shunts causing desaturation and carrying risk of
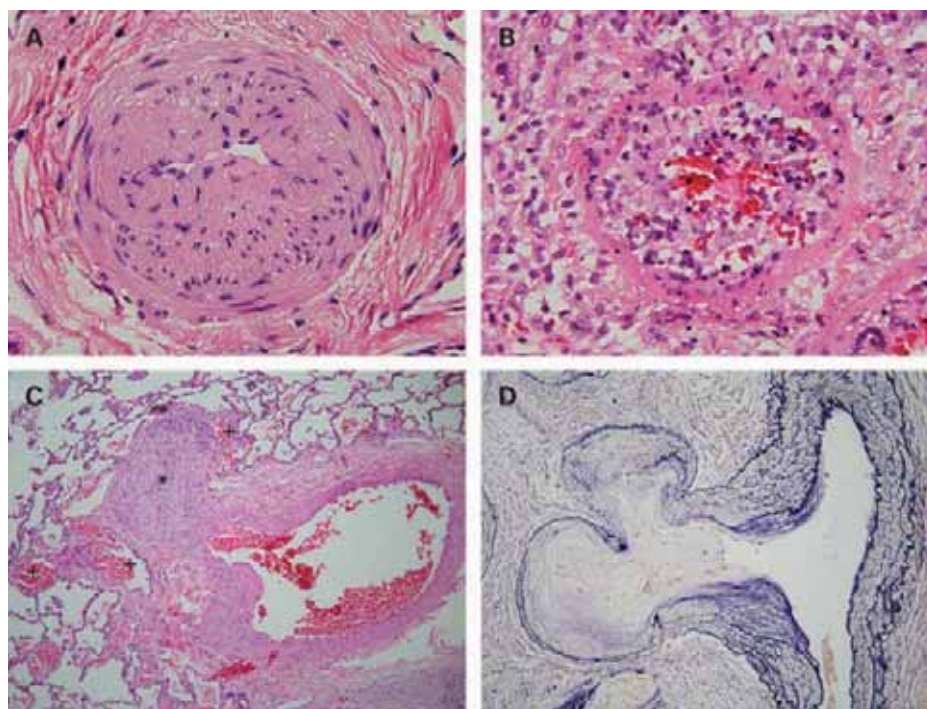
Figure 1: Pathological changes in lungs of patients with HHT and ALK1 mutation.[25] **(A) Medial smooth muscular hypertrophy including a longitudinal fascicle and intimal fibroplasia in a small pulmonary artery. (B) Necrotizing arteritis depicted by a small pulmonary artery with fibrinoid necrosis of media, intimal expansion, and mural infiltration with inflammatory cells. (C) Plexiform lesion showing excessively muscularized pulmonary artery and an aneurysm with intimal cellular fibroplasia (*) and adjacent dilated vein-like branches (+). (D) Vicinal section of pulmonary artery shown in previous image stained for elastic tissue shows aneurysm with loss of elastic lamellae and intimal massive loose fibrous expansion. Images courtesy of Harry Kozakewich, MD.** *Archives of Disease in Childhood* **by British Paediatric Association. Reproduced with permission of BMJ Publishing Group via Copyright Clearance Center.**

systemic thromboembolism or brain abscess. Genetic mutations associated with HHT were found in 80% of 194 families screened.[23] ENG mutations are more common than ALK1 mutations; however, ALK1 mutations are more frequently associated with PAH in HHT.[24] A diagnosis of HHT should be considered in children presenting with PAH as symptoms of PH have been noted to precede a diagnosis of HHT in patients carrying ALK1 mutations.[25,26] Characteristic pathological changes are found in the lungs of patients with HPAH associated with ALK1 mutation (Figure 1). Children with HHT, pulmonary AVMs, and cyanosis should be assessed for the presence of PAH prior to undergoing interventional embolization procedures.

Idiopathic PAH and HPAH in youngsters have many similar clinical charac-teristics. However, carriers of BMPR2 mutations present approximately 10 years earlier than noncarriers, have more severe disease at diagnosis, and a shorter time leading to death or need for transplant.[27] Likewise, those with HHT and an ALK1 mutation have a younger age at diagnosis and worse prognosis than those without the mutation.[24] Additionally, pediatric patients with BMPR2 mutations were much less likely to respond to acute pulmonary vasodilator testing than other PAH patients.[22]

DIAGNOSTIC EVALUATION
All patients with newly diagnosed PAH should undergo a careful diagnostic workup to identify and exclude contributors to the etiology of their illness[28] (see Figure 2[29]). This evaluation begins with a family history including detailed review seeking relatives with PAH or other cardiovascular anomalies. Particular attention should be paid to the possibility of first-degree relatives with infantile death, history of lung transplantation, exercise-related sudden death, and stigmata of HHT.

Tests performed to exclude other diagnoses such as computed tomography (CT) scans have been found to provide characteristic findings of ground glass opacities and focal hyperlucencies in pediatric patients with IPAH.[30] Sleep studies can be helpful not only by excluding sleep disorder breathing as a primary etiology of PAH, but also to diagnose superimposed nocturnal desaturation, which may contribute to disease progression in children with IPAH/HPAH. Laboratory evaluation including ESR, ANA, LFTS, and TFTS is essential to rule out associated causes of PAH.

GENETIC TESTING
Clinical genetic testing is available for BMPR2, ALK1, and ENG,[31] but this should be accompanied by genetic counseling given ramifications for other family members and low penetrance of disease. Current recommendations suggest annual clinical screening including examination and echocardiography for first-degree relatives of patients with HPAH.[31]

ASSESSMENTS OF DISEASE SEVERITY
Additional testing may be utilized to evaluate severity of disease in pediatric patients. Brain natriuretic polypeptide (BNP) levels are used to assess hemodynamic changes in children over time.[32] Magnetic resonance imaging (MRI) provides important information about right ventricular morphology and function.[33] In children, cardiopulmonary exercise testing and 6-minute walk testing are safe, reproducible, and feasible assessments of functional capacity, indicating prognosis and response to therapy.[34] Cardiac catheterization is essential in IPAH/HPAH to diagnose unsuspected structural disease and confirm hemodynamics. Patients undergo acute pulmonary vasoreactivity testing at the time of catheterization both to assist in the choice of chronic medical therapy and to inform prognosis. A posi-

Diagnostic Work-up for IPAH/HPAH
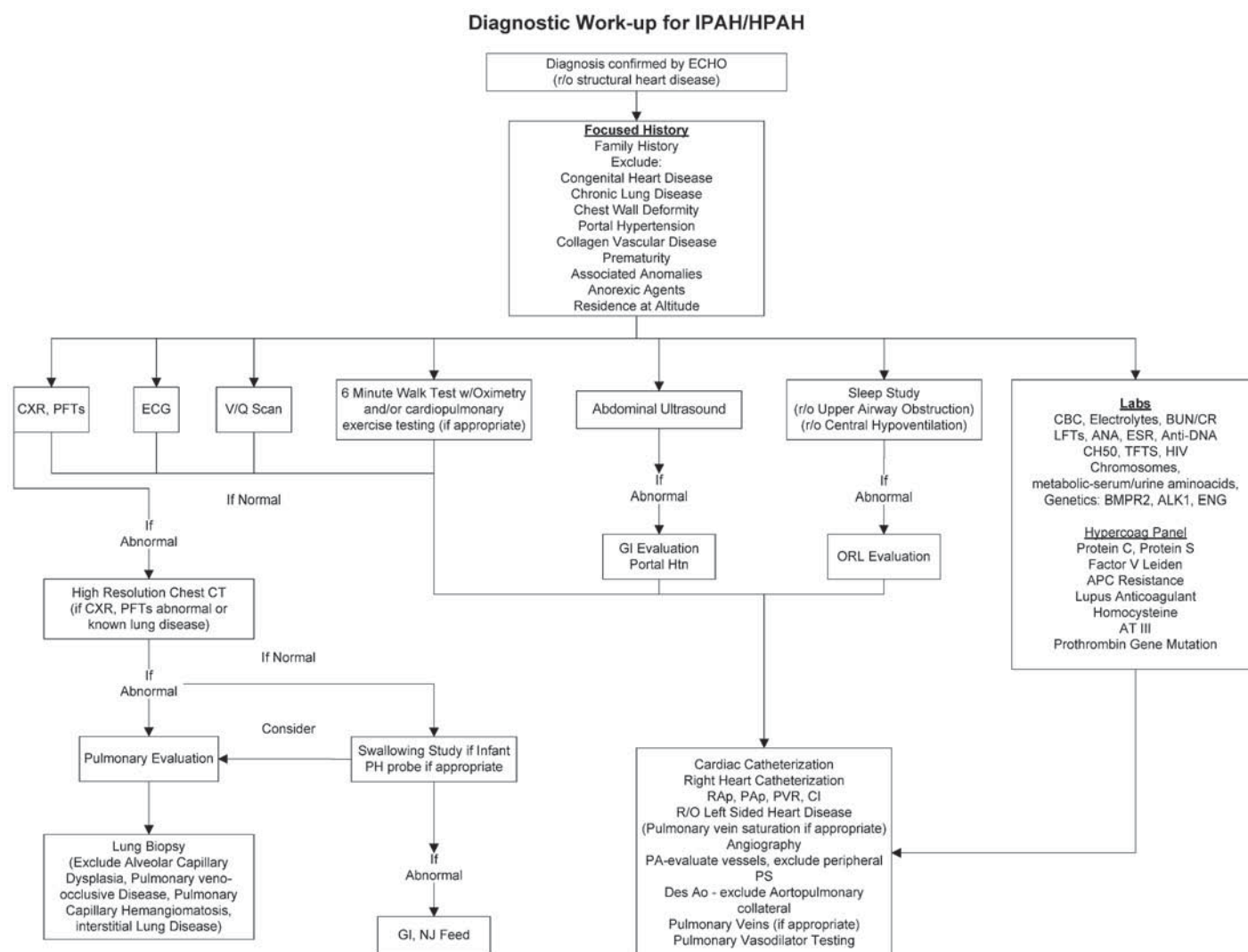
Figure 2: Diagnostic workup for IPAH/HPAH (modified).[29] CI, cardiac index; CT, computed tomography; CXR, chest x-ray; ECG, electrocardiogram; GI, gastrointestinal; NJ, nasojejuenal; PAp, pulmonary artery pressure; PFTs, pulmonary function tests; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAp, right atrial pressure. Reproduced with permission from Elsevier.

tive response to acute vasodilator testing predicts a beneficial response to long-term oral calcium channel blocker therapy.[5,35,36] The definition of response is extrapolated from adult guidelines—a decrease in mean pulmonary arterial pressure (PAP) $\geq$10 mm Hg to $\leq$40 mm Hg with unchanged or increased cardiac output.[2] Modifications of this definition have been suggested for children in whom mean PAP may be <40 mm Hg at baseline.[22,37] The choice of agents used for acute pulmonary vasodilatation may be important; a recent randomized pediatric study comparing the use of 100% oxygen, 80 PPM inhaled nitric oxide (iNO), or 80 PPM iNO/100% oxygen showed that more responders

were identified with the combination of iNO and oxygen than with either agent alone.[38] Younger patients are more likely to respond than adult patients (30%-40% vs 10%-15%), and response is predictive of improved prognosis.[38] A recent registry noted 5-year survival of 80% in children with IPAH receiving calcium channel blocker therapy[4]; however, continued close monitoring is necessary as some patients may worsen over time.[39]

THERAPEUTIC CONSIDERATIONS FOR IPAH/HPAH

Few prospective studies, and no randomized trials, have been available to guide

management of IPAH/HPAH in children. However, treatment algorithms for IPAH/HPAH have been extrapolated from adult data and modified for clinical use (Figure 3).[40] In addition to calcium channel blockers, medical therapies in current use for IPAH/HPAH include prostanoids, endothelin (ET-1) receptor antagonists, and phosphodiesterase type 5 inhibitors. Emerging data document experience with these agents in children. In pediatric IPAH/HPAH, intravenous epoprostenol has been shown to improve hemodynamics, exercise tolerance, and survival (3-year survival 94% vs 38% untreated).[38] In children, inhaled iloprost lowered mean PAP, improved functional class, and allowed some
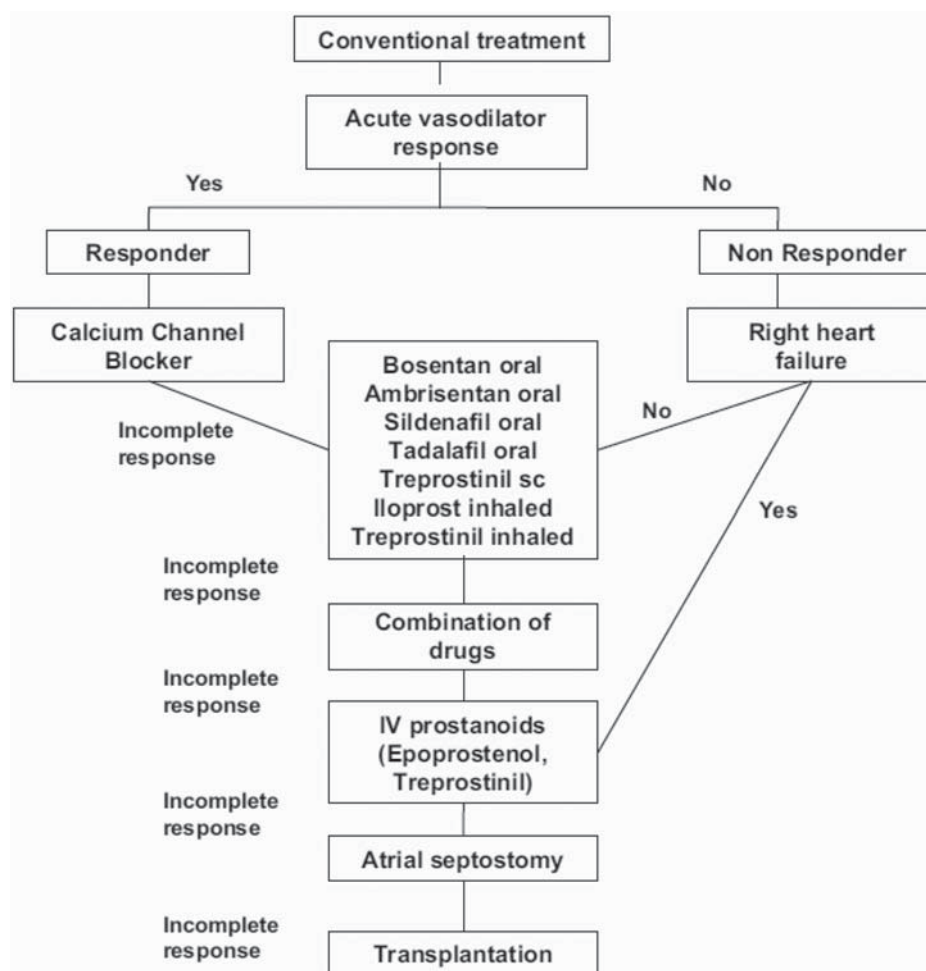
Figure 3: Treatment algorithm for pediatric IPAH/HPAH.[40] *The Journal of Pediatrics* **by American Academy of Pediatrics. Reproduced with permission of Mosby, Inc. via Copyright Clearance Center.**

patients to transition from intravenous to inhaled therapy.[41] Some pediatric patients had adverse effects associated with bronchoconstriction, and this should be closely monitored after therapy initiation. Additional options for prostanoid therapy include treprostinil with longer half-life, administered intravenously, subcutaneously, or by inhalation. Oral bosentan, a dual ET-1 receptor antagonist, has been shown to improve hemodynamics, functional class, and survival in pediatric PAH.[41,42] Ambrisentan is a single receptor ET-1 antagonist with once-daily dosing; use in children has not yet been studied. Published data on a large randomized clinical trial of outpatient oral sildenafil in pediatric patients are currently pending.

Overall strategies include initial trial of calcium channel blocker therapy in patients identified as acute responders in the cardiac catheterization laboratory. For nonresponders, patients with right heart failure are generally treated with prostanoid therapies as first-line agent. Oral endothelin receptor antagonists and phosphodiesterase 5 inhibitors may be used initially for nonresponders with mild or moderate disease. All patients should undergo reassessment with examination, echocardiography, exercise testing, and cardiac catheterization at 3-6 months after initiation of therapy. Combination therapies are frequently used for patients with incomplete response to original treatment strategy.

Atrial septostomy may be useful in pediatric IPAH/HPAH for patients with recurrent syncope despite optimized medical therapy. There has been increased interest in innovative therapies such as the reverse Potts shunt, proposed to decom-

press the failing right ventricle.[43] Lung transplant is an option for children with IPAH/HPAH. Those who received bilateral lung transplantation between 1996-2006 demonstrated survival rates of 87% and 84% at 1 and 3 years.[44]

Management of IPAH/HPAH in children requires ongoing supportive care as well as patient and family education. Supplemental oxygen and diuretics may relieve symptoms of dyspnea. Anticoagulation may prevent the development of thrombosis in situ. Pediatric patients should receive influenza and pneumoccocal vaccination according to established guidelines. Judicious exercise restriction allowing patients to self-limit may be appropriate for some children. Excellent communication with school and camp health providers as well as local emergency medical services is essential. Patients should utilize supplemental oxygen with plane travel, remain hydrated, and avoid prolonged immobilization. Families and multidisciplinary medical personnel should be alerted to the risks associated with anesthetic procedures. When developmentally appropriate, female adolescents should be informed about risks associated with pregnancy in PH.

CONCLUSION

Overall survival has significantly improved in pediatric IPAH/HPAH with recent 1- and 5-year rates estimated at 86% and 72%.[4] Insights into molecular mechanisms underlying pathogenesis of PAH may lead to targeted medical therapies affecting specific pathways of disease in the future. The development of multicenter registries will provide increased understanding of the epidemiology, spectrum, and course of IPAH/HPAH in children. Improved pediatric disease classification and development of age-appropriate outcomes will allow for improved clinical trial development. Additional prospective clinical studies of PH therapies in children will guide evidence-based practice, leading to more rational choice and combinations of medical therapies.

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