Basics of pediatric pulmonary hypertension

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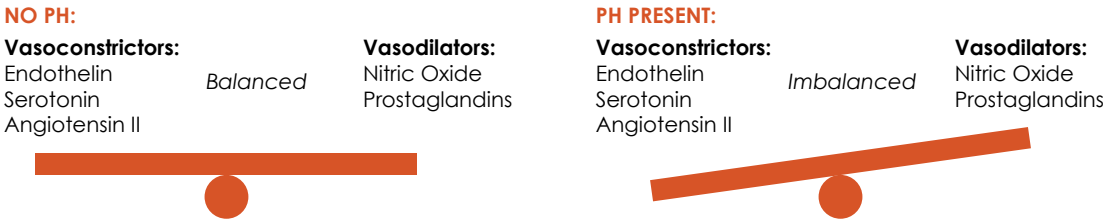
CASE DISCUSSION

A 13-year-old girl follows up with her pediatrician after an episode of syncope while running. She reports feeling more short of breath with activities and more fatigued. The pediatrician notes her to be in no acute distress, with a thin build, clear lung fields with normal saturations, and prominent precordium on exam with mild tachycardia. She has a 2/6 systolic murmur noted at the left lower sterna border that is nonradiating. Her liver edge is 2 centimeters below the costal margin, but she has no jugular venous distension. Her extremities have no edema or clubbing and she has 2+ pulses. An echocardiogram shows elevated right ventricular pressures with normal function and an otherwise structurally normal heart. After the patient is referred to cardiology, a cardiac catheterization confirms elevated pulmonary artery pressures and abnormally elevated pulmonary vascular resistance with a low wedge pressure.

Pulmonary hypertension is a complicated, multifactorial disorder. Pulmonary hypertension is clinically defined as an abnormal elevation in pulmonary vessel pressures that results in right heart pressure overload and potential right ventricular failure. Hemodynamically, pulmonary hypertension is defined by a mean pulmonary artery pressure greater than 25 mmHg when measured by catheterization (normal is around 14 mmHg). The pathogenesis of pulmonary

hypertension depends upon its etiology, but common end pathways include endothelial injury in the lung arteries resulting in smooth muscle proliferation, which encroaches upon the diameter of the artery and increases its resistance. Additionally, the balance between arterial vasoconstriction and vasodilation is offset favoring vasoconstriction, which is mediated by select vasoactive compounds (see figure 1).

Figure 1 – Balance between vasoconstriction and vasodilation can be upset in the setting of pulmonary hypertension.



The incidence of pediatric pulmonary hypertension is difficult to estimate and depends upon the etiology. Some forms of pulmonary hypertension are temporary (such as primary pulmonary hypertension of the newborn), which account for the majority of pulmonary hypertension disorders. Studies have shown an overall incidence level of about 64 cases per million children. Progressive pulmonary hypertension, such as idiopathic pulmonary arterial hypertension or persistent pulmonary hypertension as a result of congenital heart disease, occurs in 0.7 and 2.2 cases per million children, respectively.

Pulmonary hypertension used to be classified as primary (generally unknown cause) or secondary (as the result of a disease process such as unrepaired congenital heart disease). This terminology has been replaced by a classification system that groups pulmonary hypertension by associated findings and potential treatment targets. There are now six general categories of pulmonary hypertension (see table 1). The most common etiology in pediatrics is group 1, or pulmonary arterial hypertension.

Table 1 – Pulmonary hypertension classification (Dana Point 2008)

Category	Criteria
1	Pulmonary arterial hypertension • Congenital heart disease associated • Idiopathic pulmonary hypertension • Chronic hemolytic anemia associated • Persistent pulmonary hypertension of the newborn • Portal hypertension associated
2	Pulmonary veno-occlusive disease
3	Pulmonary hypertension due to left heart disease
4	Pulmonary hypertension due to lung disease/hypoxia
5	Chronic thromboembolic pulmonary hypertension
6	Pulmonary hypertension due to other mechanisms

We evaluate suspected pulmonary hypertension with the usual protocol of history, physical exam and laboratory testing. Patients who are verbal will most often complain of dyspnea on exertion or parents will note their children are notably short of breath with activities and unable to tolerate some activities. Syncope or near-syncope and chest pain (usually with exertion) are also common complaints. Children may have failure to thrive or evidence of

right heart failure with extremity edema, abdominal distension from hepatomegaly and in some cases hemoptysis. The physical exam can vary with findings seen in table 2. Patients also can have findings of certain syndromes that may place them at risk for pulmonary hypertension, such as trisomy disorders.

Table 2 – Physical findings in pulmonary hypertension

Tachypnea	Tachycardia
Prominent S2	Prominent RV heave
Murmur of tricuspid regurgitation (systolic)	Murmur of pulmonary regurgitation (diastolic)
Peripheral edema	Cyanosis
Clubbing of digits	Jugular venous distension

Diagnostic testing is centered on associated symptoms but generally includes basic tests such as chest X-ray, 12-lead EKG, blood work and echocardiography (see table 3). Possible consultation with different specialists is important to identify potential etiologies and to order the correct tests.

Table 3 – Possible labs/diagnostic test for pulmonary hypertension evaluation

Test	Rationale
Echocardiography	See below; should be done in centers with expertise in pediatric cardiology
Chest X-ray	Evaluate for lung disease, masses
EKG	Evaluate for heart strain, arrhythmias
Blood work (not exclusive list)	CBC, CMP, BNP, CRP, coagulation panel, ANA, HIV (if risk factors)
Exercise testing (if patient able): six-minute walk testing, cardiopulmonary exercise testing	Evaluate functional status, symptoms, follow therapy
Chest CT	May be used to better evaluate lung parenchyma, vascular chest lesions, masses
Pulmonary function testing	Evaluate lung capacity and respiratory status
Sleep study	Evaluate for sleep-disordered breathing
Right heart catheterization	Gold standard for diagnosis of pulmonary hypertension; allows reactivity testing

Echocardiography is one of the most important noninvasive tests to evaluate for pulmonary hypertension. Echocardiography can visualize cardiac anatomy and function that may contribute or establish patients' mortality risk. Several echocardiographic findings can suggest the presence of pulmonary hypertension such as right ventricular dilation, right ventricular hypertrophy, and flattening of the interventricular septum (see figure 2). The most important measurement is the tricuspid valve regurgitation Doppler gradient. This is an estimate of right ventricular pressure, which in the setting of no pulmonary obstruction is also the measure

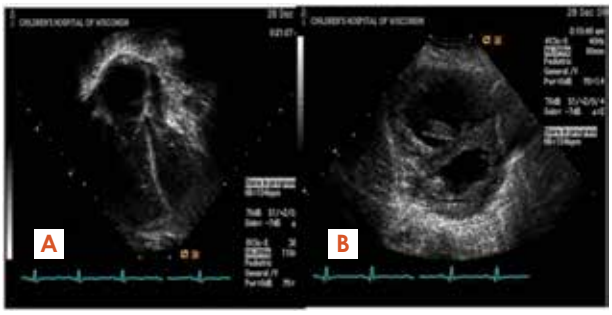


Figure 2 – A. Dilation of the right ventricle and right atrium. B. Dilation and hypertrophy of the RV (top ventricle) with interventricular flattening. These findings are consistent with severe pulmonary hypertension.

of pulmonary artery systolic pressure (plus right atrial pressure). It is important to note that echocardiography can over- or underestimate pulmonary artery pressures and therefore is not ideal for diagnosing pulmonary hypertension by itself.

Right heart catheterization is the gold standard for the diagnosis of pulmonary hypertension. Pulmonary hypertension is diagnosed when mean pulmonary artery pressures are >25 mmHg. Pulmonary artery hypertension is specifically diagnosed with associated pulmonary vascular resistance indices more than 3 Wood units and wedge or left atrial pressures ≤15mmHg. Left-side heart disease (category 2) would have higher left atrial or wedge pressures and usually low pulmonary vascular resistances. Additionally, further pulmonary artery anatomic assessment is possible using angiography. We can give supplemental oxygen or nitric oxide during the catheterization to see if this causes a significant fall in pressures (known as being reactive), which carries a better overall prognosis and directs initial therapies.

Therapies for pulmonary hypertension revolve around identifying treatable causes, such as persistent shunts and chronic lung disease. Certain diseases may require particular specialists for targeted therapies. Therapies for idiopathic pulmonary artery hypertension initially used anticoagulation, supplemental oxygen for hypoxia, and calcium channel blockers if the patient was significantly reactive by catheterization. Over the past 18 years, pulmonary hypertension-specific medications have been developed that have made a significant impact on this disease's prognosis. Figure 3 shows these drugs grouped by their pathway of action in the pulmonary artery.

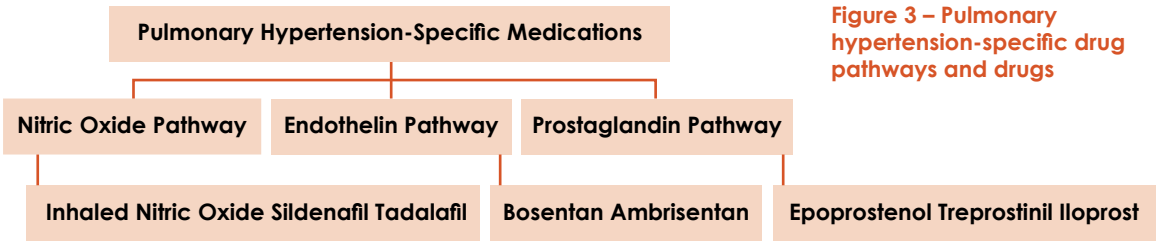


Figure 3 – Pulmonary hypertension-specific drug pathways and drugs

These drugs should only be used by physicians familiar with their indications and side effects. All are used off label in pediatrics and are designed for treatment of category 1 (pulmonary artery hypertension). Sildenafil is one of the more popular drugs used due to its oral form and ability to be compounded into a liquid for infants. This is a phosphodiesterase-5 inhibitor that is generally well tolerated with good results, though there are only limited studies regarding its use in pediatrics. In 2012, the FDA issued a black box warning about sildenafil over concerns of increased mortality in children. This has been a very controversial decision that is still being reviewed by the pulmonary hypertension community. Endothelin antagonists promote vessel remodeling. These were among the first drugs found beneficial for use in congenital heart disease, specifically Eisenmenger syndrome. They are oral medications that can be hepatotoxic and are teratogenic, thus requiring frequent laboratory follow-up and a specialty pharmacy to distribute. The prostaglandin pathway contains the most powerful drugs for treating pulmonary arterial hypertension, and those drugs are usually reserved for high-risk pulmonary hypertension patients (evidence of right heart failure or worsening symptoms on oral therapy). Epoprostenol and treprostinil require continuous IV infusion, though treprostinil also can be given subcutaneously and is now in an inhaled form. Iloprost is an inhaled agent.

Interventional procedures can be used with severe refractory pulmonary hypertension. These may include creating an atrial level shunt, usually by catheterization, to allow right to left blood flow into the left side of the heart, which will help preserve cardiac output at the expense of hypoxia. We also can create a shunt between the descending aorta and pulmonary artery to preserve cardiac output and cause only lower extremity cyanosis. The final therapy for refractory pulmonary hypertension is lung transplantation.

The prognosis for pulmonary artery hypertension as of the 1980s was quite poor. The one-, three- and five-year survival rates were 68 percent, 48 percent and 34 percent, respectively. With the use of newer medications, recent survival rates are now 86 percent, 69 percent and 61 percent for one-, three- and five-year periods, respectively. Use of multiple medications in combination and newer medications are further improving outcomes.

CASE RESOLUTION

Our patient was started on oral sildenafil and bosentan therapy. Within three months, she noted significant improvement in activity tolerance and had no further episodes of syncope. Estimates of her pulmonary artery pressure significantly improved by echocardiography and by catheterization one year later.

In conclusion, pulmonary hypertension is a multifactorial disease that can affect children of all ages and can be progressively fatal in nature. Recent medical advances have improved intermediate-term outcomes, but long-term survival benefits are unknown. A specialized multidisciplinary approach is the best way to manage this condition.

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