Pediatric Pulmonary Hypertension

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Pulmonary hypertension (PH) is a rare disease that can present in newborns, infants, and children and is associated with considerable morbidity and mortality. The etiology and presentation of PH varies substantially between children and adults. Unfortunately, the lack of sufficient controlled studies in children makes PH management challenging, with most therapeutic strategies based on extrapolation from adult studies and expert consensus.

PH is defined similarly in children and adults as a mean pulmonary artery pressure of 25 mm Hg or more at rest. The subset of such patients who have a normal pulmonary artery wedge pressure of less than 15 mm Hg are subclassified as having pulmonary arterial hypertension (PAH). PH is further subclassified according to its underlying cause, whether left heart disease, lung disease, thromboembolic disease, or a variety of other diseases. The most recent classification for PH was modified during the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension in Nice, France.

Although the exact incidence and prevalence of PH are not known, European registries have estimated the incidence to average 63.7 cases per 1 million children when including transient cases. These investigations suggest that the most common causes of transient PH in children are persistent pulmonary hypertension of the newborn and congenital heart disease (CHD). In contrast, the most common causes of persistent PH in children are idiopathic PAH and PH associated with CHD. The natural history of PH in children varies by cause, with PAH having a substantially poorer prognosis than PH with CHD.

PH is characterized by a variety of vascular abnormalities, including intimal hyperplasia, medial hypertrophy, thrombosis in situ, and varying degrees of inflammation. Endothelial dysfunction leading to imbalance of pulmonary vasoactive substances in the three pathways of prostacyclin, nitric oxide, and endothelin production is the key to the multifactorial pathogenesis of PH. Regardless of cause, as pulmonary vascular disease progresses, right ventricular dysfunction progresses, resting cardiac output decreases, and eventually right ventricular failure ensues.

Symptoms of PH are commonly nonspecific, and diagnosis may be missed in the early disease stages. Exertional dyspnea and progressive fatigue are the most frequent complaints in the older child. Symptoms are less specific in infants and may involve poor appetite, failure to thrive, diaphoresis, tachypnea, tachycardia, and irritability. Syncope, presyncope, and chest pain are features of more advanced disease, with hemoptysis being a late and sometimes fatal symptom.

The physical signs of PH include a single and loud P2 and right ventricular lift. An early diastolic decrescendo murmur of pulmonary insufficiency, a holosystolic murmur of tricuspid regurgitation, or gallop rhythm may also be audible. Prominent jugular venous distension, hepatomegaly, and peripheral edema may be present with the development of right heart failure.

Pediatric Pulmonary Hypertension. Ivy DD, Abman SH, Barst RJ, et al. *J Am Coll Cardiol.* 2013;62(25 suppl):D117–D126.

Drug Treatment of Pulmonary Hypertension in Children. Vorhies EE, Ivy DD. *Paediatr Drugs.* 2014;16(1):43–65.

Pulmonary Arterial Hypertension: A Comparison Between Children and Adults. Barst RJ, Ertel SI, Beghetti M, Ivy DD. *Eur Respir J.* 2011;37(3):665–677.

Electrocardiography may show signs of right atrial enlargement and right ventricular hypertrophy. Chest radiographs may show a prominent central pulmonary artery and peripheral "pruning" of the lung vessels. The film may also reveal signs of the underlying cause of PH, such as pulmonary veno-occlusive disease, chronic thromboembolic disease, or CHD.

Echocardiography is an extremely helpful noninvasive modality for both initial and follow-up evaluation of patients with PH. Echocardiography can be used to assess the pulmonary artery systolic pressure, right and left ventricular size and function, shunting across the patent foramen ovale, and the presence of CHD. However, definitive diagnosis of PH is established by the hemodynamic assessment and calculation of pulmonary vascular resistance by cardiac catheterization, which is still considered the gold standard on which management is based.

Additional evaluation for PH is designed to identify its underlying cause based on clinical presentation. Patients with associated signs and symptoms of pulmonary, hematologic, hepatic, gastrointestinal, rheumatologic, or infectious disease need thorough evaluation and treatment if their PH is to be controlled.

Although no single therapy can cure PH, specific targeted therapy has dramatically improved the survival of affected children. If an underlying cause for PH is identified, treatment should be directed at that cause. For example, chronic hypoxemia and obstructive sleep apnea should be aggressively treated. In addition, early recognition and treatment of respiratory infections minimize pulmonary vascular hyperreactivity. However, prevention is even better and, thus, pneumococcal and annual influenza vaccines are recommended for all patients with PH.

The goal of treatment in children is improvement in survival and quality of life, which remains a substantial challenge. There is lack of evidence in the pediatric population for targeted therapies of PH, and most treatment guidelines are extrapolated from adult data. However, drug metabolism, patient growth and development, and cause of PH are just some of the factors that differ considerably between affected children and adults.

Nonspecific conventional therapies continue to play a supportive role in the treatment of PH. Oxygen is often used to prevent hypoxemic vasoconstriction. Diuretics such as furosemide help by decreasing ventricular filling pressures. Digoxin has been shown to be beneficial in patients with PH and right heart failure by increasing contractility. Aspirin or warfarin is often used because of the increased risk of thrombosis and thromboembolism in patients with PH. Calcium channel blockers such as amlodipine relax vascular smooth muscle and can provide a survival benefit.

Several therapeutic options are available for PH associated with CHD. Inhaled nitric oxide is widely used to promote pulmonary vasodilation after cardiac surgery but only acutely in a hospital setting. For prolonged vasodilation, phosphodiesterase inhibitors such as sildenafil are commonly the first line of treatment. Endothelin receptor antagonists such as bosentan and ambrisentan, which prevent vasoconstriction, improve both exercise capacity and long-term outcome. Prostacyclin analogs have vasodilatory, antithrombotic, and antiproliferative effects on the pulmonary vasculature. Epoprostenol, treprostinil, and iloprost provide intravenous, subcutaneous, and inhalational options and have been shown to improve symptoms, hemodynamics, and overall survival.

If PH continues to worsen despite optimal medical therapy, atrial septostomy can unload the right side of the heart and improve cardiac output. This option should be considered before contemplating lung transplantation, which is the final option in the management of PH.

The outcome for children with PH has generally improved over the last few decades, and various treatment options are available, depending on the individual patient and the cause and severity of the PH. Patients may require a combination of therapies and eventually proceed to surgery despite optimal medical management. The World Symposium on Pulmonary Hypertension 2013 proposed a consensus treatment algorithm for the management of patients with PH (Figure). Irrespective of the treatments selected, children with PH require frequent follow-up evaluation with echocardiography or catheterization to assess their response to therapy as well as clinical monitoring for improvement in symptoms and quality of life.

COMMENT: If we were to judge by advertisements on television, the most common disease affecting men in the United States is erectile dysfunction. However, sildenafil, which has earned a fortune for Pfizer, was actually developed to treat angina. With the discovery that cyclic guanosine monophosphate (cGMP) is a potent intracellular vasodilator that is enzymatically degraded by a phosphodiesterase, the strategy arose to enhance cGMP concentrations by formulating a phosphodiesterase inhibitor. The real money came from what was essentially a side effect: sildenafil's activity as a vasodilator enhances blood

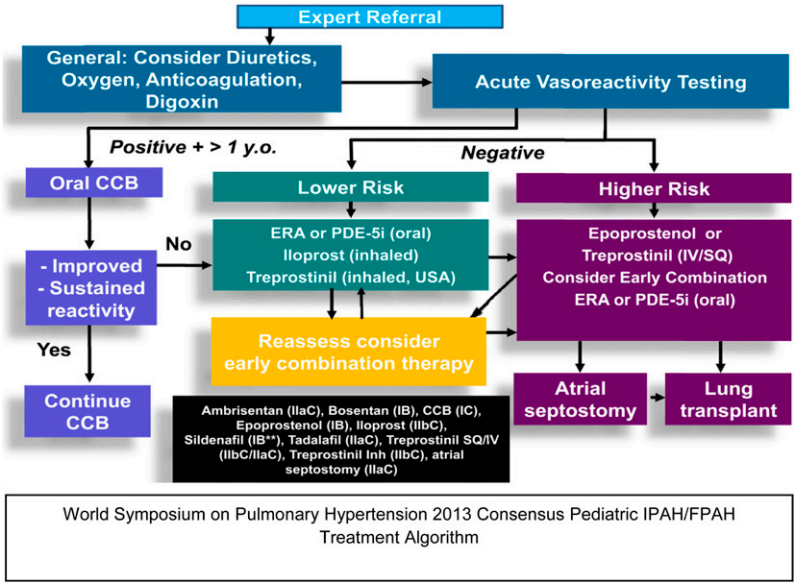

Figure. Pulmonary hypertension consensus treatment algorithm.
**Dosing recommendations per European approved dosing for children.
CCB=calcium channel blocker, ERA=endothelin receptor blocker, PDE-5i=phosphodiesterase 5 inhibitor, IPAH=idiopathis pulmonary arterial hypertension, HPAH=hereditary pulmonary arterial hypertension.
Reprinted with permission from Ivy DD, Abman SH, Barst RJ et al. Pediatric pulmonary hypertension. *J Am Coll Cardiol*. 2013;62 (25 suppl):D117–D126.

flow to the penis and, the obvious pun, gives rise to an erection. Only years after it was marketed for what has become by far its primary use was sildenafil released under a different trade name to treat PH. When was the last time you saw an advertisement on TV promoting this use for the drug?

An unrelated comment about a drug and PH: In July 2015, after this In Brief was written, the U.S. Food and Drug Administration issued a warning that diazoxide, used to treat hypoglycemia in newborns and infants, can cause PH. Apparently, once the drug is stopped, the PH is likely to abate or resolve.

And yet one more update: In November 2015, the American Heart Association and the American Thoracic Society published the first set of guidelines specifically directed at the diagnosis and management of PH in infants and children: Abman SH, Hansmann G, Archer SL, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132 (21):2037–2099. These guidelines are very comprehensive, and the contents of this In Brief are consistent with them.

– Henry M. Adam, MD
Associate Editor,
In Brief

Parent Resources from the AAP at HealthyChildren.org

- English: https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/High-Blood-Pressure-in-Children.aspx
- Spanish: https://www.healthychildren.org/spanish/health-issues/conditions/heart/paginas/high-blood-pressure-in-children.aspx
- English: https://www.healthychildren.org/English/health-issues/conditions/heart/Pages/Cardiac-Conditions-in-Teens.aspx
- Spanish: https://www.healthychildren.org/spanish/health-issues/conditions/heart/paginas/cardiac-conditions-in-teens.aspx

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