Management of Idiopathic PAH in Children: Reexamining the Evolving Treatment Algorithm

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The treatment of pediatric idiopathic pulmonary arterial hypertension (IPAH) is challenging due to the serious nature of the disease, its rapid progression, and limited treatment options available for children. Similar to adults, IPAH in children is characterized by progressive elevation of the pulmonary arterial pressure leading to right ventricular failure and clinical deterioration if left untreated. In children, disease progression appears to be more rapid. In the 1980s, prior to the current treatment era, the median untreated survival for children under 16 years of age, was reported to be as short as 10 months as opposed to 2.8 years for adults.[1] Fortunately, recent advances in the treatment of pulmonary arterial hypertension have resulted in significant improvements in the prognosis for children with IPAH. However, clinical data on pediatric pulmonary arterial hypertension is quite limited and treatment strategies are often extrapolated from adult studies. Furthermore, the selection of the optimal therapy is complex, as there are no consistently successful treatments, and some agents may involve complicated delivery systems, specific dosing regimens, side effects and potential complications. This article will review current strategies for the management of pediatric IPAH patients.

MEDICAL MANAGEMENT

Medical management of children with pulmonary arterial hypertension includes conventional therapies to treat sequelae of right ventricular failure and associated thrombosis, and targeted treatment for the pulmonary vasculopathy.

Conventional Therapy

Conventional medications that target right ventricular failure and thromboembolic events are frequently used in pulmonary arterial hypertension patients.[2] Digoxin is often used when right ventricular function is diminished, although there are no clear data documenting its beneficial effect in children. Warfarin may be used to prevent right heart thrombi and thromboemboli when right ventricular function is depressed and to prevent thrombosis in situ, commonly seen in the histopathology of pulmonary arterial hypertension. Again, the use of coumadin in children is based on studies in adults with pulmonary arterial hypertension.[3,4] Whether thrombosis in situ is a significant exacerbating factor in children in IPAH is unknown. When prescribing coumadin in children special attention should be paid to the level of activity, eg, toddlers with severe right ventricular failure require close monitoring of the prothrombin international normalized ratio (INR). Diuretics are also used to control peripheral edema and/or ascites in children with right heart failure. Oxygen therapy is indicated in cases of chronic hypoxemia to maintain systemic arterial oxygen saturation above 90%. IPAH children should be treated with supplemental oxygen when they experience systemic arterial desaturation during sleep or during an upper respiratory tract infection. Children with severe right ventricular failure and resting hypoxemia due to heart failure may also benefit from chronic supplemental oxygen.

As in adult pulmonary arterial hypertension patients, right heart cardiac catheterization with acute vasodilator testing is essential prior to selecting targeted therapy. Acute vasodilator testing is performed during cardiac catheterization and includes assessment of the acute response to a short-acting vasodilator, such as inhaled nitric oxide, intravenous epoprostenol, intravenous adenosine, or inhaled iloprost. In the past, patients were considered responsive to acute vasodilator testing if the mPAP fell 20% or more without a fall in the cardiac output.[5] While a more stringent definition was recently introduced in adults (fall in mPAP >10 mmHg to <40 mmHg) to predict long-term response to oral calcium channel blockade,[6] either definition appeared to predict long-term response to calcium channel blockade in children in a study by Yung et al.[7] Unlike adults, in whom only 7% demonstrate a robust long-term response to treatment with oral calcium channel blockade, children are more likely to have a favorable response to acute vasodilator testing and thus to long-term treatment with high-dose oral calcium channel blockers. Studies have reported up to 40% of children are responsive to acute vasodilator testing, and that

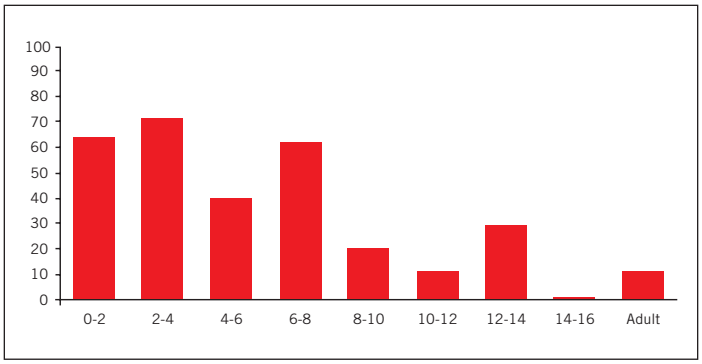

Figure 1. IPAH: Response to acute vasodilator drug testing by age. The younger the child at the time of testing, the greater the likelihood of eliciting short-term pulmonary vasodilation (P < .005).

the likelihood of response decreases with age (**Figure 1**).[5] Close monitoring of children responsive to acute vasodilator testing is still critical since the benefits observed with calcium channel blocker treatment in IPAH children who are responders (97% 5-year survival) are not always preserved over the long term (81% 10-year survival).[7] Furthermore, "treatment success" at 10 years in children who are acute responders is approximately 50% (**Figure 2**).[7] Thus, serial monitoring of these children is critical to determine whether additional treatment is warranted. Because of significant side effects (systemic hypotension, right ventricular failure), treatment with high-dose calcium channel blockers is not recommended for patients who are not acute responders and for those who have significant right heart failure.

Targeted Pulmonary Arterial Hypertension Therapy

Prostacyclin Analogues

Epoprostenol

Prostacyclin is well known as a vasodilator of the pulmonary circulation and an inhibitor of platelet aggregation. The rationale for the use of epoprostenol or other prostacyclin analogues in the treatment of IPAH is based on the imbalance between thromboxane and prostacyclin[8,9] and the decreased expression of prostacyclin synthase[10] observed in adult and pediatric IPAH patients. Intravenous epoprostenol use in children with pulmonary arterial hypertension was first described in the 1980s. In the mid 1990s, epoprostenol became the gold standard for treatment of IPAH patients who were not responsive to acute vasodilator testing, and therefore would not benefit from oral calcium channel blockers. In these patients, although there may not have been an immediate, dramatic reduction of pulmonary pressures in response to epoprostenol, long-term treatment has yielded substantial improvements in clinical status. This supports the idea that epoprostenol may have remodeling properties on the pulmonary vascular bed in addition to its role as a pulmonary vasodilator (**Figure 3**).[5]

Epoprostenol has been shown to improve hemodynamics, quality of life, and exercise capacity in patients with IPAH.[11-14] Although few pediatric studies are available, sustained clinical and hemodynamic benefits have been reported for IPAH children receiving intravenous epoprostenol for over 10 years (**Figure 4**).[5,7]

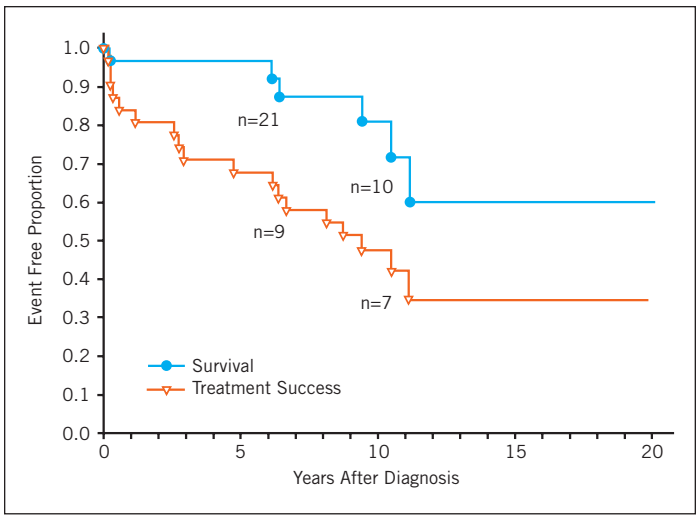

Figure 2. Kaplan-Meier curves for survival and treatment success in acute responders receiving calcium channel blockade (n = 31). Survival rates at 1, 5, and 10 years were 97%, 97%, and 81%, respectively; treatment success rates at 1, 3, 5, and 10 years were 84%, 71%, 68%, and 47%, respectively.

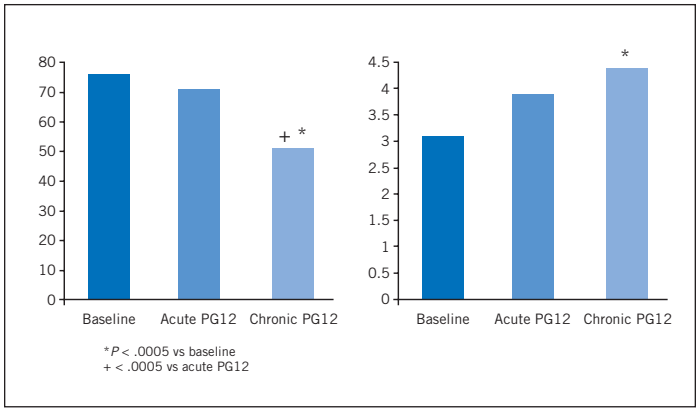

Figure 3. IPAH in children: Hemodynamic effects of acute and chronic epoprostenol (n = 27) Baseline refers to measurements before acute or chronic use of epoprostenol. Acute PGI2 was performed at the time of PGI2 testing. Chronic PGI2 measurements were taken during long-term use of PGI2 (average follow-up of 21±11 months). Adapted from Barst et al.[5]

The clinical indication for long-term continuous intravenous epoprostenol therapy is similar in children and in adults, although younger patients tend to need higher doses than adults (50 to 80 ng/kg/min after 1 year of treatment in children versus 20 to 40 ng/kg/min in adults). The starting dose is the same as for adults (2 ng/kg/min) and is uptitrated by increments of 1 to 2 ng/kg/min based on side effects and pulmonary hypertension symptoms, with the most rapid increases implemented during the first several months of treatment. Epoprostenol has a number of side effects, including jaw pain, headache, nausea, diarrhea, and foot and leg pain,[5] that are often not medically significant but that may impact a child's overall quality of life. These side effects tend to be dose-dependent and often respond to dose reduction. Because epoprostenol is chemically unstable at room temperature and has a short half-life (1 to 2 minutes), chronic intravenous epoprostenol treatment requires a continuous intravenous delivery system on ice packs. This is particularly problematic in active pediatric patients because

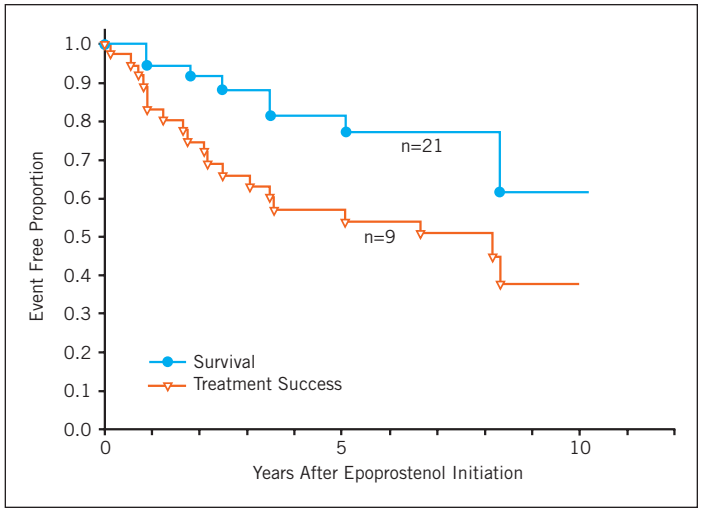

Figure 4. Kaplan-Meier curves for survival and treatment success in all patients who received epoprostenol (n = 35). Survival rates at 1, 3, 5, and 10 years were 94%, 88%, 81%, and 61%, respectively; treatment success rates at 1, 3, 5, and 10 years were 83%, 66%, 57%. and 37%, respectively.

of increased risk of line-related complications, including infections and/or dislodgement.[15] In addition, because of the short half-life of epoprostenol therapy, interruptions due to pump malfunction or line dislodgement can lead to rebound pulmonary hypertension crises that can be life threatening. The complexity of administration and side effects of epoprostenol has led to a search for alternative routes of drug delivery and to the development of prostacyclin analogues with alternate delivery systems.

Treprostinil

Treprostinil sodium is a chemically stable prostacyclin analogue with a longer half-life than epoprostenol (approximately 4? hours), which can be infused intravenously or subcutaneously. When administered acutely to IPAH patients, intravenous treprostinil has similar effects on hemodynamics as intravenous epoprostenol and induces comparable short-term decreases in pulmonary vascular resistance as subcutaneous treprostinil.[16] In a 12-week, double-blind, placebo-controlled multicenter trial involving 470 patients (including children over 8 years old) with World Health Organization (WHO) class II-IV pulmonary arterial hypertension (idiopathic or associated with connective tissue disease or congenital systemic-to-pulmonary shunts) subcutaneous treprostinil improved exercise capacity, indices of dyspnea, signs and symptoms of pulmonary arterial hypertension, and hemodynamics.[17] The risk of intravenous line infection is eliminated with subcutaneous treprostinil although pain at the site of infusion is commonly reported,[17] which may be especially troublesome for children. Topical cold and hot packs, topical and oral analgesics, and antiinflammatory drugs are variably effective in controlling these adverse effects. Common side effects also include headache, diarrhea, nausea, rash, and jaw pain. In contrast, intravenous treprostinil is a viable treatment option with a more favorable risk:benefit profile; eg, because of its longer half-life there is a decreased risk of a cessation phenomenon with rebound pulmonary hypertension. In addition, from a practical standpoint, eliminating the need for carrying ice packs along with the pump may ease the physical burden associated with a continuous intravenous infusion, particularly for children. Many patients, including some children, have now been safely transitioned from intravenous epoprostenol to intravenous treprostinil because of its favorable safety profile.[18] Treprostinil (either via subcutaneous infusion or intravenously) is currently approved in the United States for class II-IV pulmonary arterial hypertension patients.

Iloprost

Iloprost is a chemically stable prostacyclin analogue (half-life, 20 to 25 minutes) that can be used for inhaled or intravenous administration. It has both vasodilator and platelet aggregation inhibition properties similar to epoprostenol.[19,20] The hemodynamic efficacy and side effects of intravenous iloprost are also similar to those seen with intravenous epoprostenol.[21,22] Inhaled iloprost therapy is an appealing approach for the management of pulmonary arterial hypertension, given the selectivity for the pulmonary vascular bed with less systemic side effects. The first randomized, placebo-controlled study of inhaled iloprost in pulmonary arterial hypertension was performed in 203 adult patients with class III-IV pulmonary hypertension (idiopathic or associated with connective tissue disease or with inoperable chronic thromboembolic pulmonary hypertension).[23] Beneficial effects of inhaled iloprost after 12 weeks of treatment included improvement of exercise capacity, hemodynamics, New York Heart Association (NYHA) functional class and quality of life. Sustained beneficial effects have been reported after one year of treatment in adult IPAH patients.[24] In a study including 15 children with pulmonary arterial hypertension related to congenital heart defects, acute inhaled iloprost was found as effective as inhaled nitric oxide in selectively lowering pulmonary vascular resistance.[25] Common side effects reported with inhaled iloprost are headache, flushing, nausea, and dizziness. Syncope has also been reported in patients who do not have an inhalation on arising in the morning. The obvious benefit for this inhaled prostanoid therapy is that it avoids the need for a central venous catheter and its inherent risks. However, the need for six to nine treatments a day because of its short half-life may be burdensome for children.[26] In addition, the inhalation system, which requires coordination of breaths with the nebulizer device, may be challenging for children to use. Based on available data, inhaled iloprost appears as a safe, effective, and well-tolerated treatment for severe pulmonary arterial hypertension and has been approved in the United States for treatment of the disease. Although most of the studies have been performed in adult patients, this drug shows promise for patients of all ages in the future. Pediatric studies are warranted to confirm the benefits in the pediatric population.

Beraprost

Beraprost sodium is a chemically stable and orally active prostacyclin analogue. Several small, open-label, uncontrolled studies have reported beneficial hemodynamic

effects with beraprost in IPAH patients[27,28] and improved survival.[29] However, longer term studies have failed to demonstrate sustained benefit. Therefore, beraprost is not currently approved for use in the United States, although it is still often used in Japan.

Endothelin receptor antagonists

Endothelin, one of the most potent endogenous vasoconstrictors identified to date, has been implicated in the pathogenesis of pulmonary arterial hypertension, providing the rationale for endothelin antagonists for treatment of the disease.[30] Endothelin is present at elevated concentrations in the plasma and lung tissue of adult and pediatric patients with pulmonary arterial hypertension and appears to correlate with prognosis in IPAH patients.[31-33] There are at least two different receptor subtypes. ET_A receptors are located on smooth muscle cells while ET_B receptors are found predominantly on endothelial cells.[34] Both ET_A and ET_B receptors play a fundamental role in pulmonary vasoconstriction, inflammation, proliferation of smooth muscle cells, fibrosis and bronchoconstriction.

The first endothelin receptor antagonist to gain FDA approval in the United States for patients over 12 years of age is bosentan, an oral nonselective endothelin receptor antagonist that binds to both ET_A and ET_B receptor subtypes. Patients over 12 years old treated with bosentan had improvement in exercise capacity, functional class, and symptoms and demonstrated a decreased rate of clinical worsening.[35]

Bosentan is an approved therapy for pulmonary arterial hypertension patients in NYHA functional class III or IV in the United States and in Europe; however, data on bosentan therapy for pulmonary arterial hypertension in children remain limited. In a prospective open-label, non-controlled study involving 19 pediatric patients with pulmonary arterial hypertension, the safety and efficacy of bosentan appeared comparable to results previously reported in adult patients.[36] Subsequently, a retrospective analysis of 86 pediatric patients with IPAH or pulmonary arterial hypertension associated with congenital heart disease or connective tissue disease (NYHA class II-III) confirmed the safety and beneficial long-term effects of bosentan (alone or in combination with intravenous epoprostenol) on functional capacity, hemodynamics, and survival in children.[37] In 7 of 8 children with IPAH treated with intravenous epoprostenol for over one year, concomitant use of bosentan permitted a reduction in the epoprostenol dose, thereby decreasing epoprostenol side effects without apparent clinical or hemodynamic worsening.[38] In 3 of these children, the addition of bosentan resulted in the discontinuation of intravenous epoprostenol with unchanged hemodynamics for up to one year. Additional studies are required to confirm the safety of weaning or discontinuation of intravenous epoprostenol with the addition of bosentan therapy.

Sitaxsentan and ambrisentan, selective oral ET_A endothelin receptor antagonists, have been evaluated in randomized clinical trials and also appear promising for the treatment of pulmonary arterial hypertension. However, to date, these trials have not included sufficient numbers of pediatric patients for a meaningful analysis.

Adverse effects associated with endothelin receptor antagonists include acute hepatotoxicity (dose-related), teratogenicity, and possible male infertility. Common side effects reported with endothelin receptor antagonists are headache, flushing, and dose-related decreases in hemoglobin.

The clinical experience with endothelin receptor antagonists is promising for patients whose condition does not respond to calcium channel blockers. Furthermore, the possibility of combined therapy with other therapeutic agents, such as intravenous epoprostenol, intravenous or subcutaneous or inhaled prostacyclin analogues, or oral sildenafil, which have different mechanisms of action, may lead to treatment regimens with an overall enhanced efficacy and reduced dosage for each agent, ie, decreasing side effects.

Nitric Oxide and Phosphodiesterase Inhibitors

Nitric oxide is an endogenous vasodilator that relaxes vascular smooth muscle through stimulation of soluble guanylate cyclase and increased production of intracellular cyclic guanosine monophosphate (cGMP) in smooth muscle cells.[39] In patients with pulmonary arterial hypertension, nitric oxide production is often altered and nitric oxide-induced vasodilation is decreased.[40] However, the complexity of the drug delivery system for inhaled nitric oxide will likely limit its clinical development for the long-term treatment of pulmonary arterial hypertension.

In chronic pulmonary arterial hypertension, phosphodiesterase type 5 gene expression and activity are also increased,[41,42] resulting in decreased cGMP levels. Phosphodiesterase type 5 inhibitors prevent the inactivation of cGMP and may potentiate pulmonary vasodilation with inhaled nitric oxide. Sildenafil is an oral phosphodiesterase type 5 inhibitor that has recently been approved for the treatment of pulmonary arterial hypertension. Acute vasoreactivity studies in pulmonary arterial hypertension patients suggest that sildenafil may have greater acute hemodynamic effects than inhaled nitric oxide and may further reduce pulmonary vascular resistance[43] in patients already demonstrating a benefit from chronic intravenous epoprostenol.[44] Sildenafil may also prevent rebound pulmonary arterial hypertension on withdrawal of inhaled nitric oxide.[45]

In a randomized, placebo-controlled, double-blind crossover study,[46] 22 patients (aged over 12 years) with IPAH (NYHA functional class II-III) received sildenafil (25 to 100 mg three times daily, depending on weight) or placebo for 16 weeks. Patients treated with sildenafil had significantly improved exercise time on treadmill testing and dyspnea.

In the SUPER-1 trial, 278 NYHA class II-IV patients (aged over 18 years) with pulmonary arterial hypertension (idiopathic or associated with connective tissue disease or congenital systemic-to-pulmonary shunts) received placebo, 20, 40, or 80 mg sildenafil three times daily for 12 weeks.[47] At week 12, exercise capacity, hemodynamics, and functional class were improved in the sildenafil-treated patients; sildenafil was well tolerated. Randomized clinical trials evaluating sildenafil in children with pulmonary arterial hypertension are in progress.

Surgical and Interventional Treatment

Atrial septostomy

Children with recurrent syncope and signs of right heart failure who are refractory to medical treatment may benefit from atrial septostomy.[48,49] An atrial septostomy is performed during a cardiac catheterization to create an atrial septal defect which can serve as a "pop-off" valve for the hypertensive right heart (ie, permitting right to left shunting). This intervention can reduce right atrial pressure and increase cardiac output and systemic oxygen transport, improving exercise capacity and survival in IPAH patients.[49,50] Atrial septostomy may serve as a palliative bridge to heart-lung or lung transplantation. However, the procedure carries a significant risk and should be performed only in experienced centers as well as in selected patients.

Transplantation

Transplantation is the final treatment option for IPAH patients. The shortage of donor organs and the poor long-term prognosis, particularly in children, are limitations to its more widespread use. Both heart-lung and lung (single lung, bilateral lung) transplantations have been performed in pediatric patients with pulmonary vascular disease.[51] In general, most forms of pulmonary arterial hypertension, except for complex congenital heart disease, do not require heart-lung transplantation but there is currently no consensus regarding the optimal procedure.[52,53] Recent data from the Registry of the International Society for Heart and Lung Transplantation report overall 1-, 5-, and 10-year survival rates for lung/heart-lung transplantation in IPAH patients of 65/67%, 45/44%, and 20/25%.[54] Therefore, lung and heart-lung transplantation is reserved for children in whom medical treatment has failed. A general approach for transplant evaluation is to refer children who have a 2-year life expectancy of less than 50% without transplantation, or who have rare forms of pulmonary arterial hypertension, eg, pulmonary capillary hemangiomatosis and pulmonary venoocclusive disease that are not usually amenable to medical therapy.

General Measures

Although patients with IPAH have a restricted pulmonary circulation, they may maintain physical activities that are appropriate to their abilities. Patients are instructed to self-limit if they become symptomatic. Young children tend to self-limit, but parental supervision is important. Most school age children are able to partake in gym class with specific restrictions, including strict instructions to the gym instructor to allow self-limitation and pacing. Heavy weightlifting should be avoided (particularly for those at risk of syncope) in all pulmonary hypertension patients.[55] Children with advanced pulmonary arterial hypertension, particularly those with a history of syncope, are cautioned about physical activity until they are on a safe and efficacious medical regimen.

Because of the potentially devastating effects of respiratory tract infections in children with IPAH, pneumococcal and influenza immunizations are recommended in addition to staying up to date with recommended vaccinations. Other general measures include avoiding pregnancy by using effective contraception in girls of childbearing age. Oral contraception with progesterone derivatives or low-dose estrogens can be considered in patients with no history of thromboembolic disease.

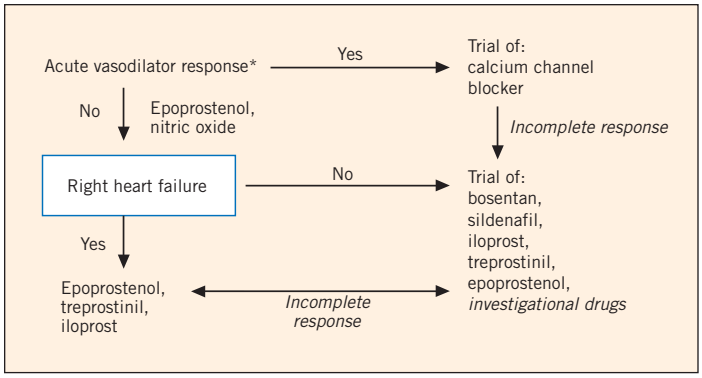

Figure 5. Clinical-based treatment guidelines for children with pulmonary arterial hypertension. *Acute vasodilator response = patient with decrease in mean pulmonary arterial pressure ≥ 20% with no change or an increase in cardiac output. Adapted from Rashid et al.[57]

Summary

A pulmonary arterial hypertension treatment algorithm based on the evidence derived from clinical trials was developed at the 2003 World Symposium on Pulmonary Hypertension.[56] This algorithm is limited to adult patients in NYHA functional class III or IV, with IPAH or pulmonary arterial hypertension associated with scleroderma because these patients represent the predominant patient population included in the clinical trials. In the absence of studies specifically reporting the clinical response of children to pulmonary hypertension therapy, similar clinical strategies have been suggested for the management of pulmonary hypertension in children. However, without evidence-based data, these guidelines should be used with caution. A general clinical approach for the treatment of pulmonary arterial hypertension in children is illustrated in **Figure 5**.[57] The initial approach following a diagnosis of pulmonary arterial hypertension in a child is to treat the child's right heart failure with digitalis and diuretics, anticoagulation with warfarin, and supplemental oxygen if clinically indicated. Patients who are responders to acute vasoreactivity testing are also treated with high-dose calcium channel blockers; nonresponders and responders who remain in NYHA functional class III should be considered for treatment with either an endothelin receptor antagonist (eg, bosentan), a phosphodiesterase type 5 inhibitor (eg, sildenafil), or a prostacyclin analogue (eg, subcutaneous treprostinil, inhaled iloprost). NYHA functional class IV patients and class III patients who do not improve with an endothelin receptor antagonist, a phosphodiesterase 5 inhibitor, or with subcutaneous or inhaled prostacyclin analogues should be considered for treatment with an intravenous prostacyclin (epoprostenol, treprostinil). With the advent of new drugs with targeted mechanisms of action, combination therapy may become an attractive option for patients whose condition fails to improve or deteriorates with a single vasoactive agent, although clinical data are currently limited. Finally,

atrial septostomy and transplantation can be considered for refractory pulmonary arterial hypertension. The treatment algorithm continues to evolve as additional treatments become available. In the future, new approaches with agents under investigation may further increase treatment options for children with this challenging disease. ■

References

1. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349.
2. Galie N, Manes A, Branzi A. Emerging medical therapies for pulmonary arterial hypertension. *Prog Cardiovasc Dis.* 2002 Nov-Dec;45(3):213-214.
3. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med.* 1992;327(2):76-81.
4. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation.* 1984;70(4):580-587.
5. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. *Circulation.* 1999;99(9):1197-1208.
6. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation.* 2005 Jun 14;111(23):3105-3111.
7. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. *Circulation.* 2004;110(6):660-665.
8. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension.1992;327(2):70-75.
9. Adatia I, Haworth SG. Circulating endothelin in children with congenital heart disease. *Br Heart J.* 1993;69(3):233-236.
10. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med.* 1999;159(6):1925-1932.
11. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;334(5):296-302.
12. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann XJ, Georgiou D, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol.* 1997;30(2):343-349.
13. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med.* 1998;338(5):273-277.
14. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40(4):780-788.
15. Widlitz A, Barst RJ. Pulmonary arterial hypertension in children. *Eur Respir J.* 2003;21(1):155-176.
16. McLaughlin VV, Gaine SP, Barst RJ, Oudiz RJ, Bourge RC, Frost A, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol.* 2003;41(2):293-299.
17. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary hypertension. *Am J Respir Crit Care Med.* 2002;165:1-5.
18. Gomberg-Maitland M, Barst RJ, Benza R, McLaughlin VV, Tapson VF. Krichman A, Rich S. Transition from intravenous epoprostenol to intravenous treprostinil in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2005;172(12):1586-1589.
19. Schror K, Darius H, Matzky R, et al. The anti-platelet and cardiovascular actions of a new carbacyclin derivative (ZK36374): equipotent to PGI2 in vitro. *Arch Pharmacol.* 1981;316:252-255.
20. Bugiardini R, Galvani M, Ferrini D, et al. Effects of Iloprost, a stable prostacyclin analogue, on exercise capacity and platelet aggregation in stable angina pectoris. *Am J Cardiol.* 1986;58:453-459.
21. Higenbottam TW, Butt AY, Dinh-Xaun AT, Takao M, Cremona G, Akamine S. Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart.* 1998;79(2):175-179.
22. Higenbottam T, Butt AY, McMahon A, Westerbeck R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart.* 1998;80(2):151-155.
23. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med.* 2002;347(5):322-329.
24. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med.* 2000;342(25):1866-1870.
25. Rimensberger PC, Spahr-Schopfer I, Berner M, Jaeggi E, Kalangos A, Friedli B, et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. *Circulation.* 2001;103(4):544-548.
26. Gessler T, Schmehl T, Hoeper MM, Rose F, Ghofrani HA, Olschewski H, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. *Eur Respir J.* 2001;17(1):14-19.
27. Okano Y, Yoshioka T, Shimouchi A, Satoh T, Kunieda T. Orally active prostacyclin analogue in primary pulmonary hypertension. *Lancet.* 1997;349(9062):1365.
28. Saji T, Ozawa Y, Ishikita T, Matsuura H, Matsuo N. Short-term hemodynamic effect of a new oral PGI2 analogue, beraprost, in primary and secondary pulmonary hypertension. *Am J Cardiol.* 1996;78(2):244-247.
29. Nagaya N, Uematsu M, Okano Y, Satoh T, Kyotani S, Sakamaki F, et al. Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol.* 1999;34(4):1188-1192.
30. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature.* 1998;332:411-415.
31. Giaid A, Yanagisawa M, Langleben D, Michell RP, Levy R, Shennib H, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med.* 1993;328:1732-1739.
32. Galiè N, Grigioni F, Bacchi-Reggiani L, Ussia GP, Parlangeli R, Catanzariti P, et al. Relation of endothelin-1 to survival in patients with primary pulmonary hypertension. *Eur J Clin Invest.* 1996;26(suppl 1):273.
33. Yoshibayashi M, Nishioka K, Nakao K, et al. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects: evidence for increased production of endothelin in pulmonary circulation. *Circulation.* 1991: 84(6):2280-2285.
34. Ohlstein EH, Douglas SA. Endothelin-1 modulates vascular smooth muscle structure and vasomotion: implications in cardiovascular pathology. *Drug Dev Res.* 1993;29:108-128.
35. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346(12):896-903.
36. Barst RJ, Ivy D, Dingemanse J, Widlitz A, Schmitt K, Doran A, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther.* 2003;73(4):372-382.
37. Rosenzweig EB, Ivy D, Widlitz A, Doran A, Claussen L, Yung D, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. *J Am Coll Cardiol.* 2005;46:697-704.
38. Ivy DD, Doran A, Claussen L, Bingaman D, Yetman A. Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. *Am J Cardiol.* 2004;93(7):943-946.
39. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature.* 1987;327(6122):524-526.

40. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med.* 1995;333(4):214-221.
41. Beavo JA, Reifsnyder DH. Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors. *Trends Pharmacol Sci.* 1990;11(4):150-155.
42. Hanson KA, Ziegler JW, Rybalkin SD, Miller JW, Abman SH, Clarke WR. Chronic pulmonary hypertension increases fetal lung cGMP phosphodiesterase activity. *Am J Physiol.* 1998;275(5 pt 1):L931-941.
43. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation.* 2002;105(20):2398-2403.
44. Kuhn KP, Wickersham NE, Robbins IM, Byrne DW. Acute effects of sildenafil in patients with primary pulmonary hypertension receiving epoprostenol. *Exp Lung Res.* 2004;30(2):135-145.
45. Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. *Anesthesiology.* 1999;91(1):307-310.
46. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol.* 2004;43(7):1149-1153.
47. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension. *N Engl J Med.* 2005;353:2148-2157.
48. Nihill MR, O'Laughlin MP, Mullins CE. Effects of atrial septostomy in patients with terminal cor pulmonale due to pulmonary vascular disease. *Cathet Cardiovasc Diagn.* 1991;24(3):166-172.
49. Kerstein D, Levy PS, Hsu DT, Hordof AJ, Gersony WM, Barst RJ. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. *Circulation.* 1995;91(7):2028-2035.
50. Sandoval J, Gaspar J, Pulido T, Bautista E, Martinez-Guerra ML, Zeballos M, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. *J Am Coll Cardiol.* 1998;32(2):297-304.
51. Boucek MM, Edwards LB, Keck BM, Trulock EP, Taylor DO, Mohacsi PJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixth Official Pediatric Report—2003. *J Heart Lung Transplant.*2003;22(6):636-652.
52. Hertz MI, Taylor DO, Trulock EP, Boucek MM, Mohacsi PJ, Edwards LB, et al. The registry of the international society for heart and lung transplantation: nineteenth official report-2002. *J Heart Lung Transplant.* 2002;21(9):950-970.
53. Franke U, Wiebe K, Harringer W, Franke T, Wittwer T, Wahlers T, et al. Ten years experience with lung and heart-lung transplantation in primary and secondary pulmonary hypertension. *Eur J Cardiothorac Surg.* 2000;18(4):447-452.
54. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult heart transplant report—2004. *J Heart Lung Transplant.* 2004;23(7):804-815.
55. Humbert M, Nunes H, Sitbon O, Parent F, Herve P, Simonneau G. Risk factors for pulmonary arterial hypertension. *Clin Chest Med.* 2001;22(3):459-475.
56. Galie N, Seeger W, Naeije R, Simonneau G, Rubin LJ. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43(12 suppl S):81S-88S.
57. Rashid A, Ivy D. Severe paediatric pulmonary hypertension: new management strategies. *Arch Dis Child.* 2005;90:92-98.