

A New Era in Medical Management of Severe Pediatric Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a life-threatening disease whose prognosis has changed dramatically over the past decade since the introduction of new therapeutic agents as well as the off-label application of adult pulmonary hypertension specific therapies to children. Nevertheless, PAH still has no cure and the aim of treatment is to prolong survival by improving quality of life, symptoms, exercise capacity and hemodynamics. The selection of appropriate therapies for PH is complex and must be carefully chosen according to the etiology and pulmonary vasoreactivity. As insight advances into mechanisms responsible for the development of PAH, the introduction of novel therapeutic agents will hopefully further improve the outcome of this incurable disease.

Introduction

Pulmonary hypertension (PH) is an important determinant of morbidity and mortality in pediatric patients. Advances in understanding the pathobiology of pulmonary arterial hypertension (PAH) have led to novel therapies; however, there remains no cure for some forms of PH, as in idiopathic pulmonary arterial hypertension (IPAH).

Definition

PAH is defined as a mean pulmonary artery pressure (PAP) ≥ 25 mmHg at rest, with a normal pulmonary capillary wedge pressure (≤ 15 mmHg) and increased pulmonary vascular resistance index (≥ 3 Woods units \cdot m²).¹⁾ A recent article reviews the clinical presentation of children with PH and outlines the difficulties of classifying pediatric PH according to this classification.²⁾ PAH may be idiopathic (pri-

mary) or heritable with no underlying cause, or associated with a specific disease (associated PAH). Most studies in children have focused on PAH associated with congenital heart disease (CHD) and IPAH.^{3–6)} PH associated with chronic lung diseases, such as bronchopulmonary dysplasia (BPD)⁷⁾ or congenital diaphragmatic hernia (CDH)⁸⁾ is increasingly recognized as an important cause of PH in the infant and child.

Clinical presentation

Diagnosis of chronic PAH is often delayed due to the subtle nature of the symptoms, which may mimic other disorders, such as respiratory disease or neurologic disease. Symptoms include exertional dyspnoea, fatigue, chest pain or syncope. In infants, symptoms are less specific and may involve poor appetite, failure to thrive, lethargy, diaphoresis, tachypnea, tachycardia, fainting while crying, and irritability.^{6,9,10)}

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1. Chest radiography

The enlargement of the central pulmonary artery and or right ventricle on chest radiography suggests the presence of PAH. Prominence of the main pulmonary arteries is apparent in most patients with IPAH. Chest radiography findings may be useful to uncover secondary causes of PH. Pulmonary venous congestion may suggest pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis; hyperinflation or kyphosis are signs of restrictive lung disease; asymmetry of the enlarged central pulmonary arteries may warrant investigation of chronic thromboembolic disease or portopulmonary hypertension.¹¹⁾ Asymmetric lung volumes may suggest either pulmonary arterial or pulmonary venous abnormalities. A unilateral small lung may be seen in unilateral “absence” of a pulmonary artery, Scimitar syndrome, or unilateral congenital absence of pulmonary veins.^{12, 13)}

2. Electrocardiography

Electrocardiography (ECG) is often the first test to suggest PAH by showing right axis deviation, right ventricular hypertrophy and right atrial enlargement. Evidence of right ventricular hypertrophy on ECG is present in most but not all children with PH. ECG findings include a qR complex in lead V_1 or V_{3R} regardless of voltage in severe cases. An upright T-wave in V_1 is indicative of right ventricular hypertrophy from 7 days to 7 years. However, some studies have suggested that the specificity (69%) and positive predictive value (67%) of ECG is low in children with an echocardiographic diagnosis of right ventricular hypertrophy (RVH).¹⁴⁾ However, the sensitivity is likely higher, especially in combination with a complete physical examination. Inverted T wave and strain-pattern ST segment are common in $V_1 \sim V_4$ in PAH patients.

3. Echocardiography

Echocardiography is the most useful non-invasive screening tool to evaluate patients with a clinical suspicion of PAH.¹⁵⁾ The echocardiogram documents right ventricular size and function, left ventricular systolic and diastolic function, morphology and function of valves, and the presence of pericardial effusion or a patent foramen ovale. The round shape of the left ventricle (LV) may change due to flattening of the intraventricular septum. The shape may change to D-shape or crescent shape. Transthoracic Doppler echocardiography can provide an estimate of the systolic pulmonary arterial pressures (sPAP). In the absence of pulmonary out-

flow obstruction, sPAP is equivalent to the right ventricular systolic pressure (RVSP). The systolic regurgitant tricuspid flow velocity (V) is measured and the right atrial pressure (RAP) is either a standardized value or an estimated value from the flow characteristics of the inferior vena cava of from jugular venous distention.¹⁵⁾ Tricuspid regurgitation of measurable quality has been reported in as many as 86% of cardiovascular patients,¹⁶⁾ but may be lower. There have been reports of a correlation between Doppler echocardiography and right heart catheterization measurements of sPAP.¹⁶⁾ However, Doppler echocardiography may underestimate sPAP in patients with severe PAH and overestimate sPAP in populations with mild or asymptomatic PAH.¹⁷⁾ Doppler echocardiography remains less accurate in most patients than invasive evaluation by right heart catheterization. Color flow Doppler imaging usually can detect intracardiac shunting although contrast echocardiography may be more suited to visualize right-to-left shunting in patients with a small atrial communication.

Recent interest has grown in the area of measurement of total right ventricular afterload by measurement of input vascular impedance. Impedance incorporates the sum of total compliance and resistance of the vascular bed.¹⁸⁻²⁰⁾ Currently, measurement of impedance requires invasive measurements in addition to measurement of Doppler flow. A recent manuscript in adults with PH showed that a measure of capacitance (pulse pressure / stroke volume) was a better predictor of survival than measurement of pulmonary vascular resistance.^{21, 22)} In children pulmonary vascular input impedance has recently been shown to be feasible and predict clinical outcomes better than pulmonary vascular resistance (PVR) in children with PAH.¹⁹⁾

4. Other evaluation modalities

Cardiac MRI provides exact measurements of heart function and blood flow and is used with increasing frequency to evaluate patients with PAH.^{23, 24)} Cardiopulmonary exercise testing using cycle ergometry or six minute walk testing has been shown to correlate with disease severity and prognosis, and is helpful in assessing responses to clinical treatments. Recently published data showed that children can safely undergo cardiopulmonary testing and the peak oxygen consumption is strongly correlated to disease severity.^{25, 26)} Six-minute walk test is a submaximal test shown to have a strong independent association with mortality among patients with IPAH; however, children often have less right

heart failure for a given elevation of PAP leading to a further distance walked. Normal values for children have recently been published.^{27, 28)}

Special situations may predispose to the development of PAH. As an example, children living at altitude and presenting with high-altitude pulmonary edema (HAPE) should be screened for PH.²⁹⁾ In addition, children with biliary atresia, cavernous transformation of the portal vein, primary sclerosing cholangitis, or cryptogenic cirrhosis, may have portopulmonary hypertension with an associated high mortality.¹¹⁾ Some medications may predispose to the development of severe PH, such as phenylpropanolamine.³⁰⁾

As respiratory disease is an important cause of PH, radiographic and physiologic evaluation of the lung should be undertaken to exclude parenchymal lung disease. This includes high resolution CT scan with contrast and laboratory evaluation for hypercoagulability and chronic thromboembolic PAH.

Cardiac catheterization is important to evaluate pulmonary artery pressures and resistance as well as to determine acute reactivity of the pulmonary vasculature.^{10, 31)} Right heart catheterization can confirm the diagnosis of PAH; assess the severity of the hemodynamic impairment, and to target therapy. The pulmonary artery pressures and pulmonary wedge pressures are measured, shunt size and pulmonary blood flow are determined and PVR is calculated by dividing the pressure gradient across the lungs by the pulmonary blood flow. Sedation may be necessary to minimize a child's agitation. Care should be taken to avoid rebound effects of inhaled nitric oxide (NO) withdrawal acutely and within 12 hours after the procedure. Pulmonary wedge angiography is quite useful to assess the appearance of the pulmonary arteries. In severe PAH patients, the "dead branches" appearance are obscure without capillary blush appearance, which may change with therapy.³²⁾

Classification¹⁾ (Table 1)

1. Idiopathic pulmonary arterial hypertension

IPAH is a rare disease which occurs most frequently in young adult females.³³⁾ IPAH, previously called primary PH, is characterized by progressive and sustained elevations of PAP without a defined etiology. While generally developing in the adult population, pediatric IPAH is well reported, and carried a dismal prognosis in the National Institutes of Health (NIH) cohort, with a median survival of only 10 months in individuals less than 16 years old.³⁴⁾ Evaluation for IPAH in the pediatric age group is similar to that out-

lined for adults and is a diagnosis of exclusion, but increased scrutiny for the possibility of congenital cardiac disease is appropriate, and acute pulmonary vasoreactivity may be more common in children.^{5, 10, 35-39)}

2. Familial – heritable pulmonary artery hypertension

Between six and 12% of cases of IPAH may be familial in origin with an autosomal dominant pattern of inheritance, with disease presenting at younger ages with subsequent generations (termed genetic anticipation).⁴⁰⁾ BMPRII is a type 2 receptor of the transforming growth factor (TGF) β superfamily of cytokines, members of which are essential for the cellular proliferation, differentiation, and apoptosis. Diverse germline heterozygous mutations in the gene that encodes for the bone morphogenetic protein receptor-II (BMPRII) cause familial PAH.^{41, 42)} These mutations appear to result in uncontrolled proliferation of vascular smooth muscle due to lack of an anti-proliferative effect of normal BMPRII signaling.^{43, 44)} More than 50 disease causing defects in the BMPRII gene have been reported, however, many have been identified in patients with no family history of PAH, implying either a low disease penetrance or the occurrence of spontaneous mutations. BMPRII was found in 6% of a mixed cohort of adults and children with PAH/congenital heart defects.⁴⁵⁾ Recent studies suggest that over 70% of patients with familial IPAH have BMPRII mutations.⁴³⁾ Mutations in BMPRII, ALK-1, endoglin and SMAD-8 have been found in children with heritable PAH.⁴⁶⁻⁴⁸⁾

Other genetic loci may also play important roles. Studies have suggested an important role of the serotonin transporter gene in some adults with PAH,⁴⁹⁾ and a study in children found that homozygosity for the long variant of the serotonin transporter gene was highly associated with IPAH in children.⁵⁰⁾

3. Congenital heart disease

A variety of congenital cardiac lesions can cause PH⁵¹⁾ (Table 2). The age at which these lesions produce irreversible pulmonary vascular disease varies. In general, patients with a ventricular septal defect or patent ductus arteriosus do not develop irreversible pulmonary vascular changes before 2 years of age, but frequently have surgery at an earlier age. Similarly, infants with an atrial or ventricular septal defect with concomitant chronic lung disease are at an increased risk for the early development of severe pulmonary vascular disease. In one study of infants with BPD who un-

Table 1 Updated WHO clinical classification of pulmonary hypertension (Dana Point, 2008)

1	Pulmonary arterial hypertension (PAH)
1.1	Idiopathic
1.2	Heritable
1.2.1	BMPR2
1.2.2	ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3	Unknown
1.3	Drugs and toxins induced
1.4	Associated with (APAH)
1.4.1	Connective tissue diseases
1.4.2	HIV infection
1.4.3	Portal hypertension
1.4.4	Congenital heart disease
1.4.5	Schistosomiasis
1.4.6	Chronic haemolytic anaemia
1.5	Persistent pulmonary hypertension of the newborn
1'	Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomas
2	Pulmonary hypertension due to left heart disease
2.1	Systolic dysfunction
2.2	Diastolic dysfunction
2.3	Valvular disease
3	Pulmonary hypertension due to lung diseases and/or hypoxaemia
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
5	PH with unclear and/or multifactorial mechanisms
5.1	Haematological disorders: myeloproliferative disorders, splenectomy
5.2	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4	Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1: activin receptor-like kinase 1 gene, APAH: associated pulmonary arterial hypertension, BMPR2: bone morphogenetic protein receptor, type 2, HIV: human immunodeficiency virus, PAH: pulmonary arterial hypertension
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derwent cardiac surgery for the repair of CHD, 25% of those who died had PAH.⁵²⁾

Patients with cyanotic congenital cardiac lesions such as transposition of the great arteries, truncus arteriosus, and univentricular heart with high flow also may develop PH. Palliative shunting operations for certain cardiac anomalies designed to increase pulmonary blood flow also may lead to the subsequent development of PH. Hypoxia with increased

shunting is believed to be a potent stimulus for the rapid development of pulmonary vascular disease.

4. Eisenmenger syndrome

Eisenmenger syndrome describes PH with a reversed central shunt.^{53, 54)} In general, the term “Eisenmenger syndrome” is used mainly for shunts distal to the tricuspid valve, but some studies have included patients with a large

Table 2 Cardiac lesions associated with pulmonary hypertension

Left-to-right shunts	Ventricular septal defect Atrioventricular septal (canal) defect Patent ductus arteriosus Atrial septal defect Aorto-pulmonary window
Increased pulmonary venous pressure	Cardiomyopathy Coarctation of the aorta (left ventricular diastolic dysfunction) Hypoplastic left heart syndrome Shone complex Mitral stenosis Supravalvar mitral ring Cor triatriatum Pulmonary vein stenosis/veno-occlusive disease Total anomalous pulmonary venous return
Cyanotic heart disease	Transposition of the great arteries Truncus arteriosus Tetralogy of Fallot (pulmonary atresia/VSD) Univentricular heart (high-flow with/without restrictive atrial septum)
Anomalies of the pulmonary artery or pulmonary vein	Origin of a pulmonary artery from the aorta Unilateral "absence" of a pulmonary artery Scimitar syndrome
Palliative shunting operations	Waterston anastomosis Potts anastomosis Blalock-Taussig anastomosis

atrial septal defect. The syndrome is characterized by elevated pulmonary vascular resistance and bidirectional or right-to-left shunting through a systemic-to-pulmonary connection, such as a ventricular septal defect, patent ductus arteriosus, univentricular heart, or aortopulmonary window. The shunt is initially left-to-right, but as the underlying condition continues to increase PVR, there is a reversal of the shunt to a right-to-left configuration, leading to cyanosis and erythrocytosis. Some patients that are detected late with Eisenmenger syndrome do not have a prior history of congestive heart failure suggesting that PVR never fell to normal levels in the perinatal period. In general, the prognosis of patients with Eisenmenger syndrome is much better than for patients with IPAH, but syncope, right-heart failure, and severe hypoxemia are similarly associated with a poor prognosis. Red blood cell depletion may be utilized in Eisenmenger syndrome to provide temporary relief of hyperviscosity symptoms or to improve perioperative hemostasis, but should not routinely be performed as this leads to in-

creased stiffness of the red blood cell.⁵⁵⁾ Non-cardiac operations on Eisenmenger patients are associated with a high mortality rate, and should be managed by a multidisciplinary team experienced in the care of patients with this condition.

5. Respiratory disease

Parenchymal lung disease is an important cause of PH in many patients. Complications include hypoxic pulmonary vasoconstriction causing increased pulmonary artery pressures and can lead to right ventricular hypertrophy and failure. Right ventricular function is usually preserved until disease is advanced. In most cases, correction of hypoxia can lead to reversal of PH. However, the development of cor pulmonale carries a poorer prognosis for reversibility.

Treatment of cor pulmonale depends on the precise etiology of lung disease, as well as disease severity. Nocturnal oxygen administration may alleviate hypoxia, typically without causing hypercapnia. Disorders of respiratory mechanics may also lead to hypoxia and the development of

PH, as can BPD.^{7, 56, 57)} More recent studies have suggested that abnormalities of the pulmonary vasculature may be a primary rather than secondary cause of abnormal alveolarization in BPD.⁵⁸⁾ Likewise patients with BPD are at increasing risk for PH in the presence of left ventricular diastolic dysfunction.⁵⁹⁾ Patients with CDH are at risk for PH, which can develop at any phases of the disease. In addition to lung hypoplasia, patients with CDH may develop pulmonary artery or pulmonary vein stenosis.^{8, 60)}

6. Thromboembolic disease

Chronic thromboembolic disease as a cause of PH in children is uncommon. However, the condition can occur rarely, and an accurate diagnosis is essential for treatment.^{31, 61, 62)} Predisposing factors include collagen vascular diseases, thrombophilia as in antiphospholipid antibody syndrome, bacterial endocarditis, and ventriculo-atrial shunt for the treatment of hydrocephalus. Likewise, the use of oral contraceptive agents may cause hypercoagulability, leading to pulmonary thromboembolic phenomena.

The diagnosis of chronic thromboembolic PH in children requires a high index of suspicion, as well as evaluation by ventilation perfusion, CT scanning, or angiography. In adults with chronic thromboembolic PH, surgically accessible disease and no severe co-morbidities, pulmonary thromboendarterectomy has been demonstrated to improve survival and quality of life.^{61, 62)} A similar approach should be considered for children who develop this condition despite the relative paucity of data on this procedure in the pediatric age group.

Pharmacological therapy of pulmonary artery hypertension

Based on known mechanisms of action, three classes of drugs have been extensively studied for the treatment of PAH: prostanoids (epoprostenol, treprostinil, iloprost, beraprost), endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), and phosphodiesterase inhibitors (sildenafil, tadalafil).⁶³⁾

Without therapy, and sometimes despite appropriate surgical correction of congenital cardiac lesions, PAH progresses at a variable rate. As vasoconstriction is an important component in the development of medial hypertrophy, vasodilators are frequently used to decrease PAP, improve cardiac output, and potentially reverse some of the pulmonary vascular changes noted in the lung. The long-term

strategy for the treatment of PH in children is similar to adults, except that it is difficult to place young children in the WHO classification.

Before commencing vasodilator therapy for chronic PAH, vasodilator responsiveness should be assessed in the cardiac catheterization unit. A positive response is defined by assessing the change of cardiac and pulmonary catheter data to vasodilators. The younger the child at the time of testing, the greater the likelihood of acute pulmonary vasodilation in response to vasoreactivity testing.^{10, 36, 64)} Many inhaled vasodilators have been used for vasoreactivity testing of vasodilator.⁶⁴⁻⁶⁶⁾

1. Calcium channel blockers

The use of calcium channel antagonists to evaluate vasoreactivity is dangerous, as these drugs can cause a decrease in cardiac output or a marked drop in systemic blood pressure.^{37, 38)} Such deleterious effects may be prolonged due to the relatively long half-life of calcium channel blockers. Consequently, elevated RAP and low cardiac output are contraindications to acute or chronic calcium channel blockade. The number of patients treated with calcium channel blockers is steadily decreasing.

Our preference is to perform an acute trial of calcium channel blocker therapy only in those patients who are acutely responsive to either NO or prostacyclin. In this setting of determination of long term therapy, response is defined as a fall in mean PAP of at least 10 mmHg to near normal levels and certainly less than a mean PAP of 40 mmHg.^{35, 63)} This criteria does not apply to determination of operability in CHD. Likewise, patients who do not have an acute vasodilatory response to short acting agents and who are then placed on calcium channel blocker therapy are unlikely to benefit from this form of therapy.⁶³⁾ 80% of children with severe PH are non-responsive to acute vasodilator testing, and therefore require therapy other than calcium channel antagonists.

2. Prostacyclins

Adults with IPAH and children with CHD demonstrate an imbalance in the biosynthesis of thromboxane A₂ and prostacyclin.⁶⁷⁾ Likewise, adults and children with severe PH show diminished prostacyclin synthase expression in the lung vasculature. Prostacyclin administered over the long term, utilizing intravenous epoprostenol, has shown to improve survival and quality of life in adults and children with

IPAH.^{38, 68, 69)} The choice of therapy for children with PAH is impacted by severity of disease, pharmacologic adverse effects, and the patients and families willingness to use invasive therapy.

Epoprostenol is a prostacyclin analogue used by intravenous infusion, shown to improve hemodynamics, quality of life, exercise capacity and survival in adults and children with IPAH.^{10, 38, 70)} Barst et al. have shown improved survival in children treated with long-term intravenous (IV) infusion epoprostenol, with a 4-year survival rate for treated children of 94%,³⁸⁾ whilst Yung et al. have reported a 10-year treatment success rate (freedom from death, transplantation, or atrioseptostomy) of 37%.¹⁰⁾ The development of tolerance is possible and most children need periodic dose escalation. The optimal dose of IV epoprostenol shows a significant patient variability, and should be titrated incrementally, with children needing usually much higher doses than adults. Adverse effects are anti-platelet activity and systemic vasodilation. Diarrhea and jaw pain are common side effects. Epoprostenol has a short half-life (1–2 min) rendering a continuous IV infusion with a permanent central venous catheter necessary. Complications like line sepsis, local infection and catheter dislodgement are not unusual and can be responsible for life-threatening rebound PH.^{71, 72)} Recently, the use of specific closed hub systems has been described in children.⁷³⁾ Alternate routes of delivery are attractive but have not been shown to be as efficacious so far.

Iloprost is an inhaled prostacyclin analogue with a longer half-life.^{74, 75)} In children treated with iloprost, WHO functional class has been shown to be improved in 35%, remained unchanged in 50% and decreased in 15%.⁷⁶⁾ Lower-airway reactivity is a problem in some children, as well as poor compliance with the need for frequent aerosol administrations (6–8 times daily). The long term efficacy of inhaled iloprost is still unknown.^{75, 77)} Iloprost has been used in post-operative CHD associated with PH⁷⁸⁾ and has been shown to be as efficacious in lowering mean PVR and improve systemic oxygen saturation compared to NO.⁶⁴⁾ Nevertheless, clinical deterioration, side effects, and poor compliance could limit its chronic administration in children.⁷⁶⁾ Alternate routes of delivery have also been tried but few data are available in children.

The prostacyclin analogue, treprostinil was approved by the USA Food and Drug Administration (FDA), initially for subcutaneous use (2002), and more recently for intravenous administration (2004) and inhaled use (2009). Subcutaneous

treprostinil has been shown to improve exercise tolerance, clinical signs, symptoms and hemodynamics in adult patients with PAH.⁷⁹⁾ Discomfort at the infusion site is common and represents the most limiting factor. No change in exercise capacity was noted in children when transitioning from intravenous epoprostenol to intravenous treprostinil but side effects were less.⁸⁰⁾ The use of IV treprostinil in children can be considered for patients who have been on a stable dose of intravenous epoprostenol with clinical improvement. Treprostinil has been studied in an inhaled form;⁸¹⁾ however little is known of its use in children.

Beraprost is an oral prostacyclin analogue, shown to improve hemodynamics and survival in adult patients with IPAH, including children.⁸²⁾ Data in children are scarce and beraprost is not available in the USA or Europe but is used in Japan.⁸³⁾ Long-acting beraprost has recently been approved for adult PAH in Japan.⁸⁴⁾

3. Endothelin

Another target for treatment of PH is the vasoconstrictor peptide endothelin (ET).⁸⁵⁾ The endothelins are a family of isopeptides consisting of ET-1, ET-2, and ET-3. ET-1 is a potent vasoactive peptide produced primarily in the vascular endothelial cell, but also may be produced by smooth muscle cells. Two receptor subtypes, ET_A and ET_B, mediate the activity of ET-1. ET_A and ET_B receptors on vascular smooth muscle mediate vasoconstriction, whereas ET_B receptors on endothelial cells cause release of NO and prostacyclin (PGI₂), and act as clearance receptors for circulating ET-1. ET-1 expression is increased in the pulmonary arteries of patients with PH. Bosentan, a dual ET receptor antagonist, lowers PAP and PVR, and improves exercise tolerance in adults with PAH.⁸⁵⁾ These results can also be extrapolated to children.^{86–90)} In children with PAH related to CHD or IPAH, bosentan lowers PAP and PVR, and is well tolerated.⁸⁶⁾ Elevated hepatic aminotransferase levels occur in approximately 11% of adults treated with bosentan. In a 12-week study children with IPAH or PAH related to CHD, bosentan was well tolerated and lowered the PAP and PVR.⁸⁶⁾ A more recent retrospective study of 86 children on bosentan for a median exposure of 14 months with and without concomitant therapy found that bosentan provided a sustained clinical and hemodynamic improvement was overall well tolerated, and two-year survival estimates were 91%.⁹⁰⁾ The safety of bosentan therapy in children with PAH has been recently reported by Beghetti et al.⁸⁶⁾ Elevated

transaminase levels were reported in 2.7% of children compared with 7.8% of patients aged ≥ 12 years, and the overall discontinuation rate from bosentan was 14% in children compared with 28% in patients aged ≥ 12 years. Bosentan has been studied in Eisenmenger syndrome in a placebo-controlled trial in patients. Bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation.⁹¹⁾ A specific pediatric formulation has been recently approved in Europe.

Selective ET_A receptor blockade is also possible using ambrisentan or sitaxsentan, ET receptor antagonists with high oral bioavailability and a long duration of action, and high specificity for the ET_A receptor. Selective ET_A receptor blockade may benefit patients with PAH by blocking the vasoconstrictor effects of ET_A receptors while maintaining the vasodilator/clearance functions of ET_B receptors. Sitaxsentan given orally for 12 weeks improved exercise capacity and cardiopulmonary hemodynamics in patients with PAH that was idiopathic, or related to connective tissue or CHD.⁹²⁻⁹⁵⁾ Ambrisentan, an endothelin receptor antagonist that is selective for the ET_A receptor was approved by the USA FDA in June 2007. Adults showed significant improvements in six-minute walk distance and significant delay in clinical worsening on ambrisentan. The incidence of elevated hepatic aminotransferase levels was 2.8%.⁹⁶⁾

4. Phosphodiesterase-5 inhibitors

Specific phosphodiesterase (PDE)-5 inhibitors, such as sildenafil,^{5, 97-109)} promote an increase in cyclic guanosine monophosphate (cGMP) levels and thus promote pulmonary vasodilation and remodeling. Sildenafil is as effective a pulmonary vasodilator as inhaled NO and may be preferred because it does not increase pulmonary wedge pressure: in patients with left ventricular diastolic dysfunction. Sildenafil may also be useful in the setting of inhaled NO therapy withdrawal^{110, 111)} in post-operative PH,¹¹²⁾ or in the presence of PH related to chronic lung disease.¹⁰⁵⁾ In some settings, intravenous sildenafil may worsen oxygenation.^{107, 113)} Studies examining the use of oral PDE-5 inhibitors in children are ongoing.^{105, 114)}

Other PDE-5 inhibitors, such as tadalafil have been recently studied leading to the USA FDA approval in 2009,¹¹⁵⁾ but studies in children are lacking. Tadalafil is also a selective PDE-5 inhibitor with a longer duration of action. No data are available in children but tadalafil has been shown to improve oxygenation in an animal model of newborn PAH.¹¹⁶⁾ In adults with severe PAH, tadalafil has been used

in combination therapy with some improvement.¹¹⁷⁻¹¹⁹⁾

5. Anticoagulation

In retrospective trials in adults with IPAH and thromboembolism, the use of warfarin has been associated with improved survival. Although the use of chronic anticoagulation has not been studied widely in children, it is usually recommended in those with severe IPAH. In IPAH, the aim is to maintain an INR between 1.5–2.0. The use of anticoagulation in patients with Eisenmenger syndrome is controversial and the potential risks and benefits of anticoagulation in this setting must be carefully weighed.

6. Novel therapies

Imatinib is a selective antagonist of the platelet-derived growth factor (PDGF) receptor and recently has shown promise in the treatment of severe PAH.¹²⁰⁾ Imatinib was approved by the USA FDA for the treatment of cancer including Philadelphia chromosome positive chronic myeloid leukemia and relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia, and Kit (CD117) positive gastrointestinal stromal tumors. PDGF has a role in vascular remodeling as PDGF participates in mitogenic signaling and smooth muscle cells recruitment. Expression of the PDGF receptor was found to be significantly increased in lung tissue from PAH patients compared with healthy donor lung tissue.¹²⁰⁾ Thus, imatinib as a potent antiproliferative agent may have a role in the treatment of PAH, a disease of lung vascular remodeling and proliferation. Case reports of the use of imatinib for patients with severe PAH refractory to all available treatment showed clinical and hemodynamic improvement and no toxic effects.¹²¹⁾ A controlled clinical trial for the use of imatinib in PAH is just beginning.

Statins have received growing attention in the treatment of PAH. Animal studies have shown dramatic responses in the prevention and regression of models of PAH. Inhibition of Rho-kinase expression and activity may be an important mechanism of the statin effect.¹²²⁾ A recent case series has suggested that this treatment requires further study.¹²³⁾

Another promising therapy is treatment with bone-derived endothelial progenitor cells (EPCs). EPCs normally function to repair and regenerate blood vessels. The delivery of EPCs to rats with established PAH resulted in marked improvement in survival, which was the greatest in the group receiving eNOS-transduced cells.¹²⁴⁾ Therefore, the

regeneration of lung vascular endothelium by injection of progenitor cells may represent a novel treatment paradigm for patients with PAH.^{124, 125)}

A novel agent, a Rho-kinase inhibitor, fausidil has also been shown to reduce PVR and may show promise for the future.¹²⁶⁾

Finally, riociguat activates soluble guanylate cyclase, stimulating the enzyme and increasing sensitivity to low NO levels. Riociguat significantly improved pulmonary hemodynamic parameters and cardiac index in patients with PH in a dose-dependent manner, and to a greater extent than inhaled NO, but was not selective for the pulmonary circulation.¹²⁷⁾

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