Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary hypertension in children

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Abstract:

Pulmonary hypertension (PH) is relatively uncommon in children. Pulmonary arterial hypertension (PAH) in pediatric comprises a wide spectrum of diseases, from a transient neonatal condition to a progressive disease associated with morbidity and mortality. Most common PAH in pediatric are idiopathic (IPAH) or PAH associated with congenital heart disease (PAH-CHD), while other associated conditions, such as connective tissue disease (CTD), are less common in pediatrics. Despite better understanding of PH and the availability of new medications during recent decades; the diagnosis, investigation and choice of therapy remain a challenge in children, as evidence-based recommendations depend mainly on adult studies.

In this review, we provide a detailed discussion about the distinctive features of PAH in pediatric, mainly emphacysing on classification and diagnostic algorithm.

Key words:

Pediatric, pulmonary arterial hypertension, specific therapy, Saudi association for pulmonary hypertension guidelines

Idiopathic pulmonary arterial hypertension and PAH-CHD are the most common types in pediatric population.[1] Most updates in our understanding of PAH pathobiology evidence-based recommendations of modern specific therapy depend mainly on adult studies.[2-4]

In 1965, Thilenius *et al*. reviewed PH in children and reported 62% fatality by 1 year after the onset of symptoms and 100% by the 7th year.[5] The median survival in untreated children diagnosed with idiopathic pulmonary hemosiderosis is <1 year.[6] Barst *et al*., have reported a median survival of pediatric IPAH patients on treatment of 90% at 4 years and 74% at 5 years.[7,8]

Extrapolation from adults to children is not straightforward for the following reasons:

1. The anticipated lifespan of children is longer.
2. Children may have greater vasodilator responsiveness and hence better therapeutic outcomes.[9]
3. The natural history is significantly worse for children compared with adult patients.[6,8]

Definition

During the 5th PH World Congress 2013, the pediatric task force agreed to keep the definition of PH in children similar to adults, and hence, PH in children is defined as mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest as measured by right heart catheterization (RHC). PAH is a subgroup of PH characterized by precapillary PH, pulmonary artery wedge pressure (PAWP) ≤15 mm Hg, and a pulmonary vascular resistance (PVR) >3 Wood units.[10-12]

Epidemiology

Data from recently published registries indicate the incidence of IPAH of 0.7-2 new cases/million child and 2.2 case/million for PAH-associated with congenital heart disease (PAH-ACHD); the prevalence of IPAH and PAH-ACHD of 4.4 and 15.6 case/million child respectively.[10-13] The female: male ratio in children is believed to be around 1.4:1.[11,13]

Classification

PH classification has evolved since 1998 reflecting better understanding of the disease biopathology. The Dana Point 2008 and subsequently Nice 2013 classification were widely accepted by pediatricians [Table 3 in the main guidelines]. Such classification has grouped PH in different categories based on disease pathobiology and characteristics.

The Pulmonary Vascular Research Institute pediatric task force has suggested the Panama classification strictly based on clinical practice, reflecting heterogeneous factors contributing to pediatric PH.[1]

During the Nice PH World Congress 2013, the Dana Point classification was modified and the persistent pulmonary hypertension in newborn (PPHN) has moved to 1" Category.

Pathobiology

The pathobiological features of PAH in children are similar to that observed in adults, and include hypertrophy of the perivascular muscular layers in small and large pulmonary arteries.

Ultimately, all three layers of the vascular wall are affected by thickening and extracellular matrix deposition, which is summarized by the term "pulmonary vascular remodeling."[14] The latter condition consists of precocious development of muscle in intraacinar arteries, proliferation of adventitial connective tissue, and medial hypertrophy of preacinar arteries.

The severity of pulmonary vascular disease (PVD) in children is classified from I to VI:

- Grade I: Media hypertrophy.
- Grade II: Cellular intimal thickening.
- Grade III: Occlusive intimal thickening.
- Grade IV: Injuries with vascular dilatation.
- Grade V: Plexiform injuries.
- Grade VI: Acute necrotizing arteritis.
- Grade I to III abnormalities are considered plexogenic (reversible), while grades IV to VI are plexiform (irreversible).

Plexiform abnormalities encompass: Hypertrophy of the tunica media of preacinar arteries, muscularization of intra-acinar arteries, concentric thickening of the preacinar arteries, complex alterations, and dilatations with arteritis.[15]

Selected Clinical Groups of Pulmonary Hypertension in Children

Pulmonary arterial hypertension

Idiopathic pulmonary arterial hypertension

Idiopathic pulmonary arterial hypertension is characterized by progressive and sustained elevations of PVR and pulmonary artery pressure (PAP) without a defined etiology. IPAH is less common in children than adults, and carries a dismal prognosis. Untreated patients <16-year-old, have a median survival of only 10 months.[6]

Evaluation for possible IPAH in the pediatric age group should be similar to that outlined for adults (please see the main guidelines), but the possibility of CHD should be carefully excluded. Obstructive sleep apnea, connective tissue and chronic thromboembolic diseases though less common in the pediatric age group, but still require exclusion. Acute pulmonary vasoreactivity may be more common in this age group compared with adults.[2,3,8]

The clinical presentation of IPAH in older children is similar to that in adults, with dyspnea on exertion, presyncope or syncope, and chest pain as prominent presentations.[2,3,8] However, presentation in infants and young children may be subtle, and may include such nonspecific findings as poor appetite, failure to thrive, lethargy, tachycardia, vomiting, and irritability.[16] Acute vasoreactivity test (AVT) is crucial prior to initiation of treatment; AVT responders have a better long-term prognosis whether on mono- or combination-therapy.[3,8,17,18]

Heritable pulmonary arterial hypertension (HPAH)

Mutations to cause HPAH, e.g., BMPR2 are reported in 10-16% of childhood-onset PAH and in 21-26% of adult onset.[19] The cause in childhood appears to be heterogeneous in nature, with genetic defects of transforming growth factor-beta receptors and epigenetics contribute to the disease.[20]

Please refer to the review of "genetics in PAH" in this issue of the journal for more details.

Pulmonary arterial hypertension associated with congenital heart disease

Congenital heart disease is relatively common, affecting around 1% of children. Within this population, 10% will go on to develop PAH.[21]

In utero PVR is high, but falls at birth rapidly to near normal levels allowing the pulmonary perfusion and gas exchange. The PVR continues to fall gradually over the 1st month of life.[16]

Pulmonary arterial hypertension can occur in children with CHD with large left-to-right shunt and high pulmonary blood flow. PH in CHD can be either hyperkinetic or secondary to venous hypertension, [Table 1]. Hyperkinetic PH refers to PAH from congenital systemic-to-pulmonary communications with increased pulmonary blood flow, such as ventricular septal defect (VSD) or patent ductus arteriosus (PDA). PVH is caused by disorders of the left-heart filling, such as mitral stenosis, pulmonary venous obstruction, or left ventricular (LV) failure. CHD causing pulmonary venous hypertension in children include total anomalous pulmonary venous return with obstruction, left heart obstruction, or severe LV failure. The lungs of those born with left inflow obstruction show pronounced thickening in the walls of both the arteries and the veins, and the outcome depends on the results of the surgical intervention. Progressive long-segment pulmonary vein hypoplasia leading to pulmonary venous atresia is another uniformly fatal condition presenting in infancy with severe pulmonary venous hypertension.

Pulmonary veno-occlusive disease (VOD) has a distinct pathological feature of uniform fibrotic occlusion of peripheral small pulmonary venules.[22] Although, it is a form of pulmonary vascular obstruction, it is not routinely included under CHD, as it can be acquired. Currently, it is considered in the classification guidelines as a separate entity as Group 1'. VOD is rare in children, but can occur early in childhood and has been reported in familial cases.[23]

A variety of CHDs can cause PAH.[9] Age at which these lesions

Table 1: Different form of PH in CHD in children

Type	Classification
Hyperkinetic (PAH-ACHD)	$P = F \times r$
Pulmonary vascular obstruction or venous hypertension	$P = f \times R$

P: pulmonary artery pressure; *F*: pulmonary blood flow (high); *r*: total pulmonary resistance (normal); *f*: pulmonary blood flow (normal); *R*: total pulmonary resistance (high)

cause irreversible PVD also varies. In general, patients with VSD or PDA do not develop irreversible PVD before the age of two. Children with Down's syndrome may have increased risk of PAH if CHD is also present. Infants with atrial septal defect or VSD with concomitant chronic lung disease are at increased risk of early development of severe PVD. In one study of infants with bronchopulmonary dysplasia (BPD) who underwent cardiac surgery for repair of CHD, it was shown that 25% of those who died had PAH.[24] Patients with cyanotic CHD, such as transposition of the great arteries, truncus arteriosus, and single ventricle with unrestricted pulmonary flow may also develop PAH. Palliative shunt operations for certain cardiac anomalies designed to increase pulmonary flow may also lead to subsequent development of PAH. Hypoxia with increased shunting is believed to be a potent stimulus for rapid development of PVD. Total correction of many cardiac lesions in the first few months of life may prevent the late development of PAH. Eisenmenger syndrome describes the state of PAH with reversed central shunt.[25] The term is used for shunts distal to the tricuspid valve and characterized by elevated PVR and bi-directional or reversed shunt through a systemic to pulmonary connection, such as VSD, PDA, or univentricular heart. Prognosis of patients with Eisenmenger syndrome is much better compared with IPAH. Syncope, right heart failure, and severe hypoxemia are associated with poor prognosis.

Further details about patients' selection and operability in CHD are discussed in the "PAH-ACHD" review in this issue of the Journal.

Pulmonary arterial hypertension associated with connective tissue diseases

Pulmonary arterial hypertension is a well-recognized complication of CTDs, such as systemic sclerosis and SLE. The prevalence of PAH in patients with CTD has been reported to be as high as 38%.[26] In systemic sclerosis, pulmonary complications, such as interstitial lung disease and PAH, are now the leading causes of death. As in adults, patients with PAH associated with systemic sclerosis have a particularly poor prognosis compared with those with systemic sclerosis without PAH.[26]

Pulmonary arterial hypertension associated with HIV infection

Pulmonary arterial hypertension is rare in HIV patients' population, with estimated prevalence of 0.5%.[27] HIV-associated PAH shows a similar clinical picture to IPAH and seems to be independent of the degree of immunosuppression.

Pulmonary Hypertension Due to Respiratory Diseases

Disorders of respiratory mechanics may lead to hypoxia and the development of PH. Various developmental lung anomalies are recognized as the etiology of PH, such as surfactant protein deficiencies, lung hypoplasia, congenital diaphragmatic hernia, alveolar capillary dysplasia, pulmonary alveolar proteinosis, pulmonary interstitial glycogenosis, and pulmonary lymphangiosis.[24,28] Recent studies on BPD patients have suggested that abnormalities of the pulmonary vasculature may be a primary rather than secondary cause of abnormal or decreased alveolarization. In addition to high vascular tone barotraumas altered abnormal smooth muscle proliferation has been recognized as a contributing factor in the development of PVD in BPD.[24,28]

Children with congenital diaphragmatic hernia are at risk for PH, which can develop at any phase of the disease. In addition to lung hypoplasia, patients with congenital diaphragmatic hernia may develop pulmonary artery or pulmonary vein stenosis.[15,29] Obstructive sleep apnea is less commonly encountered in the pediatric age group, but still require exclusion.[30]

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Chronic thromboembolic pulmonary hypertension is uncommon in children. However, the condition can occur rarely, and an accurate diagnosis is essential for treatment as it is the only curable form of PH.[31] Predisposing factors include collagen vascular diseases, thrombophilia, bacterial endocarditis, and ventriculo-atrial shunt for the treatment of hydrocephalus. The diagnosis of CTEPH in children requires a high index of suspicion.

Diagnostic Evaluation of Pulmonary Hypertension in Children

To assess a child with PH, relevant investigations should be focused to:

1. Determine the cause.
2. Assess the severity.
3. Assess the response to treatment.

Determine the cause

Successful evaluation of PAH includes a comprehensive history and examination to differentiate among underlying etiologies. Family history should be thoroughly investigated. Children with biliary atresia, cavernous transformation of the portal vein, primary sclerosing cholangitis, or cryptogenic cirrhosis, may have porto-PH, which is associated high mortality.[32] Drug use should also be investigated. History of exposure to high altitude, repeated respiratory infections, obstructive sleep apnea, thromboembolic events, and neonatal antecedents.

The routine for diagnostic evaluation may include a series of supplementary tests adapted to the individual clinical requirements. Such diagnostic tools include radiological and physiological assessment.

Radiological tests

High-resolution computerized tomography is an essential diagnostic tool for the evaluation of lung parenchyma, underlying pulmonary disease, and to detect pulmonary VOD.

Magnetic resonance imaging (MRI) may provide information on the size and function of the right ventricular (RV), myocardial thickness, pulmonary artery morphology, pulmonary and cardiac pressures and presence of chronic thromboembolism.[33,34] However, MRI usually require sedation in children, and its rule in PAH management has not yet been established.

As in adults, the ventilation/perfusion (V/Q) lung scan is the most useful screening test for CTEPH and should be performed before the diagnosis of CTEPH is ruled out.

Exercise tests

6-min walk test (6-MWT) is difficult to perform in children younger than 5 years of age. In older children, it should be routinely performed as it provides important assessment and prognostic parameters (see main guidelines).

Ergometric cardiopulmonary exercise test (CPET) should ideally be undertaken at the time of diagnosis to establish baseline impact on function. It can also be done during follow-up to assess the response to treatment. Similar to 6-MWT, CPET can be performed in patients 5 years and older. Rhodes *et al*. have reported that exercise capacity correlated with right atrial pressure, PAP, and cardiac index, and that it was useful in predicting prognosis and survival.[35] Furthermore, peak oxygen consumption (VO_{2max}) has been shown to correlate with PVR measured by RHC. VO_{2max} of <15 ml/kg/min predict worse outcome or need for additional pharmacological therapy.[35]

Transthoracic Doppler echocardiography (TTE)

Transthoracic Doppler echocardiography is a noninvasive test that can be useful for screening and assessing prognosis. Transthoracic echocardiographic estimates is also important in estimating systolic PAP (sPAP) and to evaluate potential structural abnormalities, such as congenital or acquired heart disease.[7,11,16]

Mild PH is objectively defined as a sPAP of 40-50 mmHg, corresponding to a tobacco rattle virus of 3.0-3.5 m/s. Posterior bowing of the interventricular septum into the LV Chamber causing D-shaped LV cavity occurs with significant PH. Posterior bowing of the interatrial septum is seen with elevation of right atrial pressure.

The presence and size of a shunt through an anatomical interatrial communication can be identified by contrast study by two-dimensional echocardiography. The rate of disappearance of bubbles injected into the right atrium can be useful as a qualitative assessment of right heart function and resting cardiac output (CO).[13,36,37]

The parameters that should be obtained by echocardiography are summarized in Table 2.

Right heart catheterization

Right heart catheterization is considered the gold standard for the diagnosis of PAH. All patients should undergo RHC for the measurement of:

- Right atrial pressure.
- PAP (mean, systolic and diastolic).
- PAWP.
- CO.
- Calculated PVR.
- Systemic and pulmonary arterial oxygen saturation.
- Mixed venous oxygen saturation and pulmonary venous oxygen saturation in patients with congenital heart defects.
- Vasoreactivity testing.

Table 2: Echocardiographic parameters and measurement in PH

Echocardiographic measurements
Tricuspid regurgitant velocity
Pulmonary artery systolic flow acceleration time
Right ventricular ejection time
Right ventricular dimensions
Right ventricular volumetric data
Right ventricular index of myocardial performance
Timing of mid-systolic deceleration of right ventricular ejection
Size of blood flow through defect
Direction of blood flow through the defect

Vasodilator testing

Similar to adult patients, the following short-acting vasodilators are recommended for acute testing: Inhaled nitric oxide (iNO), intravenous epoprostenol, or inhaled iloprost.

A positive acute vasoreactive (acute vasodilator response [AVR]) is defined as:

1. Barst criteria, 1986: Decrease in mPAP of ≥20%, unchanged or increased cardiac index, and decreased or unchanged pulmonary to systemic vascular resistance ratio (PVR).
2. Rich criteria, 1992: Decrease in mPAP and PVR of ≥20%;

Sitbon criteria, 2005: Decrease in mPAP of ≥10 mmHg reaching a mPAP ≤40 mmHg and an increased or unchanged CO.

Most pediatric cardiologists use the Barst criteria.[37] Compared to adults, children have a greater rate of vasoreactivity response.[7,11] However, in both children and adults, AVR is associated with improved survival independent of the used criteria.[37-40]

Long-term vasodilator drug treatment can be initiated on the basis of AVR testing. Studies have shown that patients with IPAH who have a reactive pulmonary vascular bed also responds to calcium channel blockers (CCBs).[39,40] Children who do not manifest acute responsiveness to vasodilators are unlikely to have clinical benefit from oral CCBs therapy and may actually deteriorate if oral CCBs are attempted.

The risk-benefit ratio should always be taken into account when performing RHC for pediatric patients with severe PH. Special precautions, such as adequate sedation and prevention of hypovolemia and hypoxemia, should be taken.[11,35]

Table 3 summarizes the high-risk parameters in pediatric PH patients:

Table 3: High-risk parameters in pediatric patients

Risk parameters
Clinical
Failure to thrive
Syncope
Progressive disease
Modified NYHA functional Class III, IV
Echocardiography
RV dysfunction
Pericardial effusion
Hemodynamic
RAP >10 mmHg
PVRI >20 wood units/m^2
RVEDP >15 mmHg

NYHA = New York heart association, RV = Right ventricular, RAP = Right atrial pressure, PVRI = Pulmonary vascular resistance index, RVEDP = Right ventricular end diastolic pressure

Therapeutic Options

General principles

Management strategy should be based upon an attempt to selectively dilate the pulmonary vascular bed to improve RV function, and so increasing pulmonary blood flow. Better understanding of the regulation of pulmonary vascular tone leads to the appropriate use of drug combination.[6]

Exercise and immunization

Increased oxygen demand may aggravate PH; nevertheless, appropriate level of physical activities and rehabilitation is recommended (class of recommendation: I). Respiratory infections should be treated and prevented. Immunization for influenza (flu-vaccine), respiratory syncytial virus, and pneumococcus is recommended (class of recommendation: I).

Fluid management and diuretics

Children with PH accompanied by signs of documented RV failure and hepatic and systemic congestion might obtain some benefit from diuretics therapy (class of recommendation: I). However, great caution must be taken to avoid the risk of hypovolemia, which would affect the RV filling and worsen CO.[7]

Oxygen therapy

Continuous oxygen therapy is indicated for all hypoxemic children.[21] Children who exhibit reduced oxygen saturation during the night may also benefit from the administration of nocturnal oxygen. Patients with Eisenmenger syndrome, however, do not seem to benefit from this treatment, although nocturnal oxygen therapy might delay the progression of polycythemia.[21,41]

Oxygen therapy is recommended for children during long travel or symptomatic respiratory infections.[38] When oxygen therapy is indicated, the objective is to maintain oxygen saturation above 90%, except in those patients who have cyanotic CHD (class of recommendation: I).

Anticoagulation

Anticoagulation is recommended to prevent the risk of thromboembolism in specific cases, such IPAH, reduced CO, indwelling veno-atrial shunt or severe polycythemia. Similar to adult patients, the aim of anticoagulation is to maintain International Normalised Ratio between 1.5 and 2.0. Anticoagulation in children might be more cumbersome compared to adults.

Specific drug therapy

Detailed discussion about specific drug therapy in PAH can be found in the article of "specific treatment for PAH" in this issue of the Journal. In the following discussion, we will only emphasize on specific pediatric recommendations.

Calcium channel blockers

Calcium channel blockers therapy should be attempted only in patients who demonstrated positive vasoreactivity. Those patients have generally better prognosis and better survival. Elevated right atrial pressure or low CO are contraindications to CCBs therapy.[4]

Inhaled nitric oxide

Inhaled nitric oxide is an inhaled vasodilator with a selective action on pulmonary circulation. It activates the guanylyl cyclase enzyme in pulmonary smooth muscle vascularization, which increases cyclic guanine monophosphate (cGMP) and reduces intracellular calcium concentration, resulting in vasodilation.[11] It is not yet known whether iNO has antiproliferative properties in the pulmonary vascular bed.[42,43] The use of iNO for persistent PPHN and for the management of CHD-APAH during the immediate postoperative period are well-established,[6,15] while the prophylactic use of iNO for patients at risk of PH during the postoperative period for the correction of CHD is still controversial. Treatment should be discontinued after 30 min, if there has been no clinically significant response.

Phosphodiesterase-5 inhibitors (Sildenafil)

Sildenafil is a selective type five phosphodiesterase inhibitor, which promotes an increase in cGMP levels causing pulmonary vasodilatation and inhibit remodeling.[44,45]

Sildenafil is available as 20 mg (Revatio®) and 25 mg (Viagra®) tablets. Dosage should start at 0.1 mg/kg, with stepwise increases by 0.1 mg/kg up to 0.5 mg/kg every 6 h.

However, in patients with cardiac disease, initial dosage may be as high as 0.5 mg/kg every 6 h, with stepwise increases by 0.1 mg/kg up to 1.0-1.5 mg/kg.

Schulze-Neick *et al*. compared the effects of IV sildenafil to iNO in 24 children with PAH-ACHD. Intravenous sildenafil was more effective for reducing PVR than was iNO.[46] However, the selective pulmonary vasodilator effect of sildenafil was associated with increased intrapulmonary shunt. Although, this was clinically insignificant in this study, it could, however, represent an undesirable effect in the postoperative period for CHD patients.

Of note, the Food and Drug Administration (FDA) has recommended that sildenafil not be prescribed to children (ages 1 through 17) for PAH. This recommendation against use is based on a long-term clinical pediatric trial showing that children taking a high-dose of sildenafil had a higher risk of death than children taking a low dose.[47] However, despite the higher mortality in the high-dose group compared to the lower-doses groups, the survival rate in that particular group was much higher than the historical control, and the high observed mortality can be probably explained by the more severe disease in this group. Hence, both the European Medicines Agency (EMA) and the Saudi Association for Pulmonary Hypertension (SAPH) have issued a statement recommending to continue using sildenafil in pediatric patients. This recommendation was based on the revision of the pediatric clinical trials that did not identify any new safety signal that would appear to be specific to the pediatric population. The adverse event profile for sildenafil in pediatric PAH trials was consistent with the adverse event profile of sildenafil in adult PAH clinical trials, and both agencies have recommended to continue using sildenafil in the pediatric population. Approved dose of sildenafil by EMA and SAPH is 10 mg 3 times daily for weight <20 kg and 20 mg 3 times daily for weight >20 kg. High-doses should probably be avoided in the pediatric patients until more safety data are available.

Endothelin receptor antagonists

Bosentan is a nonselective dual endothelin (ET) receptors ET-A and ET-B antagonist. It has shown to improve symptoms, exercise performance, and hemodynamics in PAH patients. It is available as 62.5 and 125 mg tablets. It has been approved for use in adults for the treatment of primary PAH.

Data on bosentan in the pediatric population are limited. Barst *et al*.[48] performed an open uncontrolled study involving 19 patients at two centers. These patients had functional Class II or III and weighed >10 kg. A 13% reduction in mPAP was observed. However, no changes were observed in the walking distance or functional class. Apparently, the pharmacokinetic and hemodynamic effects of bosentan were similar to those observed in adult patients. The FDA has approved the drug for use in children over 12 years or with weight >40 kg on the basis of this study.

Rosenzweig *et al*. performed a retrospective study involving 86 children with PAH of varying etiology. They were given long-term bosentan (14 months) in isolation or concurrently with prostacyclin. The children were evaluated in terms of hemodynamic variables and modified NYHA functional class. There was a significant improvement in hemodynamics and in functional class in 46% of the patients.[49]

Bosentan starting dose in pediatric is 1 mg/kg twice a day for the 1st month; if liver function is stable, the dose can then be increased to 2 mg/kg twice a day.

Ambrisentan is a selective ET-A receptor antagonist with high oral bioavailability and long duration of action.[50] The drug action is based on the blockage of the vasoconstrictor effect of ET-A receptors, while maintaining vasodilation and clearance of ET-B receptors. The risk of hepatotoxicity is much less compared to bosentan, and liver function monitoring is not recommended.

Prostacyclin

The use of prostacyclin (epoprostenol) or prostacyclin analogs for the treatment of PAH is based on the imbalance between thromboxane and prostacyclin metabolites.[51] Prostacyclin induce relaxation of the respiratory vascular musculature, stimulating the production of cyclic adenosine monophosphate, and inhibit respiratory muscle cell growth and platelet aggregation.[38] It appears that the chronic benefits from their use are associated with an antiproliferative property.[38]

Epoprostenol has demonstrated good results in children with severe IPAH, PAH-ACHD, and PAH HIV-APAH).[15]

Parenteral administration of prostacyclin is complex, because it requires a "fully implantable" intravenous catheter for continuous infusion. Several adverse effects have been reported that include maxillary pain, headaches, diarrhea, nausea, leg pains, and complications associated with the infusion system. This complex delivery process is more difficult to handle in children compared to adult patients.

Iloprost is an inhaled prostacyclin analog. Its small particle size guarantees its pulmonary selectivity.[38] However, its short half-life (45 min) demands frequent administrations between 6 and 9 times/day. The clinical experience in children is still limited. The dose varies depending upon the response of each patient.

Treprostinil used as a subcutaneous infusion, which has a longer half-life and increased stability. Limited clinical experience in children showed improved hemodynamics and functional class in patients with refractory PAH.[52]

Combined treatment

The combined use of drugs, which have different sites of action, appears to be promising for PAH treatment. Adjuvant use of drugs with different mechanisms of action has been shown to improve many prognostic variables.[53-55]

Atrial septostomy

Children with frequent syncope and RV heart failure have a poor prognosis. Exercise-induced syncope occurs secondary to the inability to increase CO to maintain cerebral blood flow. Atrial septostomy allows right-to-left shunting leading to improvement in RV function and so improvement of the left heart filling, and CO.[57] Risks of the procedure include worsening of hypoxemia, RV ischemia, worsening RV failure, increased left atrial pressure, and pulmonary edema. Survival rate of 87% and 76%, at 1-and 2-year, respectively, has been reported.[58]

Lung transplantation

Lung transplantation is restricted by long waiting time, risks of surgery, transplant rejection, and availability. Table 1 illustrates the high-risk patients with poor survival who should be considered for lung transplantation. Due to a better outcome, double lung transplantation is the current standard of care. Pediatric data from the International Society for Heart and Lung Transplantation demonstrate 2-year survival of 65% and 5-year survival of 50%.[59-61]

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