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Diagnosis and Management of Pulmonary Arterial Hypertension in the Pediatric Population (PH)

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Pulmonary arterial hypertension (PH) is a rare disease that affects either sex at any age. It is frequently under-diagnosed and many patients present with prolonged interval between onset of symptoms and diagnosis, which delays their treatment and shortens their prognosis yet further. Mortality associated with PH is extremely high. Once the diagnosis has been confirmed, mean survival among adults is 2.8 years and less than one year among children. Advances in the understanding of the mechanisms involved in the patho-biology of PH associated with other conditions have focused on molecular biology, developmental biology and genetics. Together with epidemiological and natural history studies, collaborative efforts between the scientific community and the industry have led to a surge in clinical trials over the past decade with six new medications which are approved by the FDA that lead to improvement in the median survival, Quality of life, 6 minutes walk test, functional class and delayed progression of the disease.

In this review, we discuss the recent diagnostic and treatment modalities which are appropriate to the pediatric population.

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The true incidence of pulmonary arterial hypertension (PH) is unknown, but it is calculated that 1-2 new cases of primary PH per million inhabitants in the general population[1,6]. Secondary PH is relatively more common, but frequently under-diagnosed. Usually there is a prolonged interval between onset of symptoms and diagnosis of PH, which delays the treatment and worsens the prognosis yet further[1,6]. Mortality associated with PH is extremely high. Once diagnosis has been confirmed, the mean survival among adults is 2.8 years and less than one year among children.

Over the last few years, advances have been associated with earlier diagnosis and a greater understanding of the pathophysiological mechanisms involved. Now, we understand better the association between the degree of vascular compromise and the clinical manifestations presented. These findings have changed both the survival and the quality of life of these patients. Nevertheless, in the pediatric population the disease behaves differently.

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Increased reactivity of pulmonary vessels is an obstacle for achieving better prognosis established for adult patients. In contrast, this increased reactivity may result in better prognosis in the future, in the event that these patients come to benefit from the clinical use of new drugs (with vasodilatory and anti-proliferative effects)[1-6].

Definition of Pulmonary Hypertension (PH)

The definition of PH is derived from adult patients and includes all individuals with mean pulmonary arterial pressures >25 mm Hg at rest or >30 mm Hg with exercise no matter what age (British Cardiac Society Guidelines and Medical Practice Committee, 2001). Since most of these measurements are performed by echocardiography, tricuspid regurgitation with a Doppler velocity of more than 2.5 m/sec has been used for the screening for PH. Most pediatric cardiologists would agree on a definition of PH where systolic pulmonary artery pressure exceeds 50% of systolic systemic pressure. These measurements are usually taken from either tricuspid regurgitation or from any known connection between systemic and pulmonary circulation (i.e. patent ductus arteriosus, ventricular septal defect[1]).

Incidence: Conflicting data have been published concerning the incidence of PPHN. Some reported an incidence of 0.2% in live-born term infants; others gave a higher range of 0.43-6.8 per 1000. The associated mortality rate of PPHN at the beginning of the 21st century was given at 10-20%, whereas earlier studies reported mortality rates of up to 50%.

Classification: The WHO classification of PH was modified lately in 2003 (Proceedings of the 3rd World Symposium on Pulmonary Arterial Hypertension, 2004) as the following, Table 1[1-11].

Table 1: Classification of Pulmonary Hypertension (Children and Adults)

Group	Type
Group I Pulmonary arterial hypertension (PH)	Idiopathic (IPH) Familial (FPH) Associated with (APH) Collagen vascular disease Congenital systemic-to-pulmonary shunts Portal hypertension HIV infection Drugs and toxins **Other** (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy). Associated with significant venous or capillary involvement.

	Pulmonary veno-occlusive disease (PVOD) Pulmonary capillary hemangiomatosis (PCH) PPHN
Group II PH with left heart disease	Left-sided atrial or ventricular heart disease Left-sided valvular heart disease
Group III PH associated with lung diseases and/or hypoxemia	Chronic obstructive pulmonary disease Interstitial lung disease Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental abnormalities
Group IV PH due to chronic thrombotic and/or embolic disease	Thromboembolic obstruction of proximal pulmonary arteries Thromboembolic obstruction of distal pulmonary arteries Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
Group V Miscellaneous	Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Specific Disease Association

Pulmonary Arterial Hypertension (PH) associated with connective tissue disease: PH is a well-recognized complication of connective tissue diseases such as systemic sclerosis and SLE and in affected patients may also occur in association with interstitial lung disease. The prevalence of PH has been reported to be up to 38%[7]. In systemic sclerosis patients with, pulmonary complications such as interstitial lung disease and PH, are now the leading causes of death. Patients with systemic sclerosis in association with PH have a particularly poor prognosis compared to those without PH[3].

Pulmonary Arterial Hypertension (PH) associated with congenital heart disease: Congenital heart disease is relatively common, affecting around 1% of the population. Within this population, 10% will develop Pulmonary Arterial Hypertension (PAH)[8]. A variety of physiologic factors contribute to the severity and rate at which vascular disease develops in patients with congenital heart defects. Lesions at high risk include transposition of the great arteries (TGA) with intact ventricular septum, a large ventricular septal defect (VSD), large atrial septal defect (ASD) and patent ductus arteriosus (PDA). Even after successful surgical correction of TGA in infancy, there have been case reports of progression of pulmonary vascular disease. Infants with a VSD and especially those with an atrioventricular septal defect can also develop severe irreversible

pulmonary vascular disease as in Eisenmenger's syndrome causing cyanosis and limited exercise capacity[1-9].

Pulmonary Arterial Hypertension (PH) associated with HIV infection: PAH is a rare but relatively well-documented complication of HIV infection (estimated prevalence in patients with HIV is 0.5%)[10]. With the advent of highly active anti-retroviral therapy (HAART) and markedly improved survival, PAH and other non-infectious manifestations of HIV infection are increasingly responsible for HIV-associated morbidity and poor prognosis. In patients with HIV, the HIV-1 envelope glycoprotein GP120 may stimulate the production of endothelin by macrophages[11]. HIV-associated PH shows a similar clinical picture to idiopathic or primary PH and seems to be independent of the degree of immunosuppression.

Pulmonary Arterial Hypertension (PH) associated sickle cell disease: The prevalence of PAH in patients with sickle cell disease (SS) is 20%-40%[5]. In autopsy studies, approximately 75% of patients with SS present histological evidence of pulmonary hypertension. In another study in SS patients with PH in a 22-month follow-up period, 40% mortality rate, with odds ratio of 7.86 and 95% confidence interval (95% CI) of 2.63-23.4[6].

The pathogenesis is multi-factorial, including hemolysis, impaired nitric oxide bioavailability, chronic hypoxemia, thrombo-embolism, chronic liver disease and asplenia[5].

Porto-Pulmonary Hypertension: Is the development of PH associated with increased pulmonary vascular resistance complicated by portal hypertension, with or without advanced hepatic disease. The incidence of PH is 2% in patients with portal hypertension, mortality of 40% at one year and 70% at 3 years for isolated liver transplantation.

It is postulated to be due to high cardiac output and hyperdynamic circulatory state, with increased stress on the pulmonary circulation, in addition to injury to the vascular endothelium.

Another mechanism was thought to be due to splanchnic volume overload and bowel-wall congestion, which leads to increased release of endotoxins and cytokines (endothelin-1 and thromboxane) which constrict the blood vessels[12].

Schistosomiasis and PH: Chronic *schistosomiasis* causes severe liver fibrosis secondary to hepatosplenic *schistosomiasis*, which leads to portal hypertension (hepatopulmonary syndrome) and ultimately corpulmonale. It is due to endothelial damage in the pulmonary circulation that results from diverting of *Shcistosoma* eggs through porto-systemic shunts[13].

Familial primary pulmonary hypertension (FPPH): It is caused by mutations in bone morphogenetic protein receptor II (BMPR2), which maintains small vessel integrity.

FPPH has the same clinical and pathological characteristics as sporadic PPH. Both have similar ages of onset and 2:1 female to male ratio. FPPH was reported as 6% of 187 cases in the NIH registry. It can occur from infancy throughout life (mean age 36.4 years in NIH registry) making longitudinal follow-up necessary. FPPH families have been widely spread geographically but are predominantly Caucasian, although families of Afro-American, Indian and Asian descent have been affected. It is inherited as an autosomal dominant disorder with reduced or incomplete penetrance[14].

Physiological Factors That Influence Pulmonary Artery Pressure[1]

1. Carbon dioxide and hydrogen ion concentration: Alkalosis produces pulmonary vasodilatation and acidosis results in pulmonary vasoconstriction. In a study of children with trisomy 21 and increased propensity to PH following the atrioventricular valve repair, pulmonary vascular resistance (PVR) decreased in spite of high PaCO2, confirming hydrogen ion concentration to be the primary determinant of PVR[1,15].

2. Oxygen: An increase in PVR occurs only below an alveolar oxygen tension of about 60 mmHg. The pathophysiological mechanism of hypoxic pulmonary vasoconstriction (HPV) is thought to be due to the Redox regulation of O2-K-sensitive channels of mitochondrial sensors in resistance artery, and smooth muscle cells (SMC). Similarly, the low PO2 environment favors inuteropulmonary vasoconstriction, whereas increased alveolar PO2 secondary to the first few breathes instantaneously vasorelaxes the pulmonary circulation[1,15].

3. Lung Volume: During anesthesia or resuscitation, at low lung volumes, PVR increases because of the surrounding uninflated lungs compressing intrapulmonary blood vessels. As the lungs are expanded, PVR falls and is lowest at the functional residual capacity. However, with overdistension, PVR increases again as a result of stretching the intrapulmonary vessels[1,15].

4. Nitric oxide: Nitric Oxide (NO) is synthesized in the vascular endothelium by nitric oxide synthase (NOS), via the oxidation of the terminal guanidino nitrogen atom of the amino acid L-arginine (LA). NO relaxes smooth muscle cells (SMC) by activating the soluble enzyme guanylate cyclase; therefore, increasing the intracellular cyclic guanosine 3'-5' monophosphate concentrations initiating a cascade that results in relaxation of the arterial smooth muscle. It relaxes smooth muscle under normal conditions. It also causes relaxation under hypoxic and hypercapnic conditions[1,15].

5. Endothelins: Endothelins (ET) are a family of potent vasoactive modulators, which also mediate SMC proliferation in the vascular wall. ET1 is found in the highest concentration and acts on both Endothelin A (ET-A) and Endothelin B (ET-B) receptors. ET-A receptors are responsible for vasoconstriction, whereas ET-B receptors are responsible for vasodilatation and clearance of ET1. Increased concentrations of ET1 have been demonstrated in children with PAH. Studies have demonstrated that ET1 concentrations correlated with pulmonary reactivity in response to hypoxia. Endothelin

antagonists, both non-specific blockers of ET-A and ET-B receptors, and specific ET-A antagonists reduce PVR and improve symptoms[1,15].

It appears that an "imbalance" takes place between vasoconstrictor and vasodilator mediators (increased thromboxane and reduced prostacyclins, increased endothelin and reduced NO). Other factors which may also be involved are: serotonin, growth factor-derived platelets, angiotensin and loss of vascular NO and prostacyclin due to synthesis genetic expression. The initial endothelial damage results in recruitment of local vasoactive mediators, provoking a procoagulatory state, leading to consequent vascular obstruction. Furthermore, defects in pulmonary circulation smooth muscle potassium channels also appear to be involved in onset and/or progression of PH[6].

Pathology: Most prominent histologic changes in persistent pulmonary hypertension of the newborn (PPHN) include hypertrophy of the perivascular muscular layer in small and large pulmonary arteries. Ultimately, all 3 layers of the vascular wall are affected by thickening and extracellular matrix deposition, which is summarized by the term ‘pulmonary vascular remodeling’. 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 can be classified into:

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). 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 and ferrugination[6].

Signs and Symptoms: Symptoms of infantile PH include breathlessness, fainting or chest pain during exercise, and exercise-induced syncope. A minority of infants presents with cyanosis, hemoptysis, or right heart failure with ankle edema or hepatomegaly.

Irrespective of etiology, patients with PH do not exhibit a specific clinical status. Smaller children predominately exhibit symptoms of low cardiac output (failure to thrive, lethargy, irritability, tachypnea and tachycardia). Older children describe a certain degree of respiratory distress, fatigue and headaches (especially from light) and may suffer chest pain (from right ventricular ischemia), episodes of syncope triggered by exertion and, in certain cases, sudden death. Invasive anesthetic and sedative procedures are not well-tolerated, and patients with Eisenmenger syndrome may exhibit episodes of hemoptysis[6,16-19].

Eisenmenger's syndrome is defined as vascular pulmonary disease related to congenital heart disease. In these patients vascular disease develops after a hyperkinetic period, with normal vascular resistance and increased pulmonary blood flow[16].

Clinically, patients present with pale extremities (due to low cardiac output) and cyanosis (due to low oxygenation) because of intrapulmonary or intracardiac (L-R) shunts via the foramen ovale[16].

Some infants may suffer convulsions as a result of exaggerated pulmonary vasoconstriction, but this is a rare complication. In these patients, systemic arterial oxygenation may be reduced during sleep (especially during the first few hours of the morning)[16].

The interval between the onset of symptoms and diagnosis is significantly shorter in children. It is rare for the signs of direct heart failure to emerge in children less than 10 years old. In these cases, peripheral edema and acrocyanosis are the signs of terminal disease.

In pediatric patients, cardiovascular auscultation is not rich, but the pulmonary component is always more audible. Signs of tricuspid regurgitation may be present, and even thoracic deformity may be observed, secondary to severe right ventricular hypertrophy[16,20].

Functional Classification[6]

Patients with PH can be classified according to their functional capacity (degree of functional limitation):

Class I: Patients with PH and no limitation of Physical activity: Physical activity does not cause dyspnea, chest pain, tiredness or syncope.

Class II: Patient with PH and mild limitation of physical activity: Patient is comfortable at rest, Everyday physical activity causes dyspnea, chest pain, tiredness or near syncope.

Class III: Patient with PH and marked limitation of physical activity: Patient is comfortable at rest. All and any physical activity causes dyspnea, chest pain, tiredness or near syncope.

Class IV: Patient with PH incapable of any physical activity whatsoever without causing symptomatology: Patients with signs of heart failure. Dyspnea and/or fatigue may be present at rest. Distress is increased by any physical activity whatsoever.

Diagnosis

General History: Diagnosis of PH is by exclusion, but there maybe a high degree of clinical suspicion. Family history should be thoroughly investigated for: connective tissue disorders, relatives with PH, congenital heart disease, other congenital malformations and any history of sudden death in the family. Drug use should also be investigated (especially psychotropics and appetite suppressants) as should exposure to altitude, repeated respiratory infections, obstructive sleep apnea (not so rare in children), thromboembolic events (rare in pediatrics) and neonatal antecedents[16,20,21].

The routine diagnostic evaluation may include a series of supplementary tests adapted to the individual clinical requirements of each patient[6].

Chest X-ray: Widened pulmonary trunk and proximal bronchial branches, with discrepant thinning of peripheral branches ("tree branches" appearance), is highly suggestive of PH.

Pulmonary function test (PFT): May be normal, but must be performed in order to rule out pulmonary lung disease.

Gasometry tests or (Blood gas analysis): Gasometry (or just oximetry) analysis at rest and post-exercise can be useful for tracking disease progression[6, 22].

Laboratory assessment: Initial tests include complete blood count, prothrombin time, activated partial thromboplastin time, liver function tests, autoimmunity panel and HIV test[23].

Echocardiogram (ECHO): A sensitive non-invasive diagnostic method, it is the first examination to be performed with color Doppler in patients with clinical suspicion of PH[6,23]. The echocardiogram evaluates right ventricular function, which traces the progressive damage resulting from the disease, and is of fundamental importance for sequential monitoring of PH[6,22-25]. It excludes cardiological causes of PH, such as right ventricular dysfunction, mitral valve disease and the presence of intracardiac shunt[6]. The measurement of tricuspid regurgitation velocity enables the estimation of right ventricular pressures.

Transthoracic Doppler echocardiogram: It is used to estimate systolic pressure in the right ventricle (RV) by means of tricuspid regurgitation velocity measurements. The pressure is estimated from a right atrial pressure plus pressure gradient from tricuspid value regurgitant velocity[23]. This figure offers good correlation with systolic pressure at the pulmonary artery[27]. However, it is well known that RV systolic pressure can be underestimated in patients whose tricuspid regurgitation velocity is reduced[6,26,27].

Computerized tomography: Indicated for differential diagnosis of PH patients. The high resolution CT scans has brought the technical results comparable to pulmonary angiography[28].

Cardiac catheterization: Is considered the gold standard for the diagnosis of PH. Practically all patients with PH should undergo right cardiac catheterization for the measurement of PAP (mean, systolic and diastolic), pulmonary capillary wedge pressure, cardiac output, oxygen saturation and to calculate pulmonary vascular resistance (PVR) and shunts. PVR, cardiac output, and central venous saturation are the most important prognostic parameters in PH. Cardiac catheterization also evaluates pulmonary vascular response to vasodilators: a fall in PAP to below 40 mmHg, a drop of more than 20 mmHg, or of more than 20% of baseline are considered positive hemodynamic response (response test)[6,18,20].

The severity of PH is classified as: mild (P_mAP from 25 to 40 mmHg), moderate (P_mAP from 41 to 55 mmHg) or severe (P_mAP > 55 mmHg)[26]. Cases of PH secondary to heart disease or chronic lung disease are generally related to mild to moderate increases in pulmonary pressure. Patients with severe PH are generally suffering from PPH, connective tissue disease, or chronic thromboembolism[6]. Some patients with mild to moderate PH, secondary to chronic hypoxemia, pulmonary pathologies or collagen disorders, can be monitored serially with echocardiograms (every 3 to 6 months) and cardiac catheterization can be reserved for those cases that pass functional class III according to the New York Heart Association (NYHA) scale[6]. Catheterization is particularly indicated to rule out congenital heart disease, occult shunts and stenosis of the distal pulmonary artery. The risk-benefit ratio should always be taken into account when indicating cardiac catheterization for pediatric patients.

Angiotomography (ventilation/perfusion or V/Q lung scan): The most useful screening test for pulmonary thromboembolism. One or more perfusion segments or defects tomography is a finding highly suggestive of thromboembolism (“moth-eaten” appearance). In PPH, angiotomography is normal[6,23].

Magnetic resonance imaging: Provides information on the size and function of the RV, myocardial thickness, presence of chronic thromboembolism and pulmonary and cardiac pressures.

Pulmonary angiography: Indicated for patients with chronic thromboembolic pulmonary hypertension, primarily in potentially-surgical cases, for which it aids in locating the embolism and defining its extent.

Pulmonary biopsy: Biopsy is reserved for cases where histopathological diagnosis is necessary, such as vasculitis, granulomatous disease, veno-occlusive disease or interstitial disease[6].

Walking test: A simple test that offers good correlation of patient survival. Should be undertaken at the time of diagnosis to establish baseline impact on function; during follow-up it can assess response to treatment and prognosis. It can be performed on patients five years and older[6].

Therapeutic Options

1. General: The aim is to maintain sufficient pulmonary blood flow and avoid complications, until resolution of the raised PVR. The aim is to improve alveolar oxygenation, minimize pulmonary vasoconstriction, and maintain systemic pressure and perfusion. Complications may result either from hypoxia or from barotrauma. The degree of hypoxia depends upon the ratio of PVR to systemic resistance.

Increased oxygen demand may aggravate PH and diastolic heart failure (DHF); therefore, physical activities are restricted (risk of effort syncope)[29]. Respiratory infections should be treated and prevented by immunization for influenza (flu-vaccine), pneumococcal vaccine (Prevenar) and Respiratory Syncytial virus (RSV vaccine) named Synagis or Palivizumab, which is a monoclonal antibody produced by recombinant DNA technology.

2. Alkalosis reduces PVR; muscle relaxants, sedation, and aggressive hyperventilation to render the infant alkalotic have been used. Rapid ventilation rates with high peak pressures produce a higher minute volume with low arterial carbon dioxide, producing a respiratory alkalosis. In a study, of children with PPHN, it was demonstrated that a sudden precipitate increase in PaO2 once a pH of 7.55 was reached. However, this pH required a PaCO2 between 2.6 and 3.9 kPa (20–30 mmHg). Although PVR may be lowered by alkalosis, lung injury may result from the relatively hard ventilation that is required, worsening the long-term outcome[3].

3. Digitalis and diuretics: Patients with PH accompanied by signs of documented right ventricular failure and low pulmonary flow (DHF), with hepatic and systemic congestion, should obtain some benefit from reduced after load and a certain inotropic effect, but great care must be taken because of the risk of concomitant preload reduction, which would worsen cardiac output[17].

4. Oxygen therapy is recommended for patients with PH secondary to parenchymatous pulmonary disease. Patients with Eisenmenger's syndrome or PPH do not appear to benefit from this treatment, although nocturnal oxygen therapy may delay progression of Polycythemia in those who have Eisenmenger's syndrome[17]. Children who exhibit reduced oxygen saturation during the night (in the absence obstructive disease or apnea) may benefit from the administration of nocturnal oxygen. During these episodes patients may present with severe crises of dyspnea and syncope, with or without convulsive hypoxemic crises[17]. Continuous oxygen may be indicated for children with severe DHF, with hypoxemia during sleep, and markedly elevated oxygen extraction[17]. It is recommended for patients who will travel by air or have symptomatic respiratory infections, because of the risk of triggering PH crises[18]. When oxygen therapy is indicated, the objective is to maintain oxygen saturation above 90% (except in those patients who have cyanotic congenital heart disease)[29].

5. Inhaled nitric oxide: It is a vasodilator with selective action on pulmonary circulation. It activates the guanylyl-cyclase enzyme in pulmonary smooth muscle vascularization, which increases cyclic guanine monophosphate (GMPc) and reduces intracellular

calcium concentration, resulting in vasodilation[16]. Administered by inhalation, NO rapidly binds to hemoglobin in pulmonary capillaries, inactivating it. This makes it a selective pulmonary vasodilator, capable of attenuating the pulmonary vasoconstriction induced by hypoxia or other vasoconstriction agonists, without producing significant systemic vasodilation. It is not yet known whether NO has anti-proliferative properties in the pulmonary vascular bed[18]. The use of NO for persistent PH in the neonate and for the management of congenital heart disease (especially during the immediate postoperative period) are well-established[6,30]. Prophylactic use of NO for patients with risk of PH during postoperative period after correction of congenital heart disease is controversial.

The European consensus recommendation is to start at 20 ppm and observe the response for 10 minutes. Sequentially increase to 40 ppm and observe the response over a short period of time, around 30 minutes (no more than 2 hours). The response criteria are a reduction in PAP and/or at least 20% improvement in oxygenation saturation over the baseline. Patients who do not respond to 40 ppm will probably not respond to 80 ppm either. As soon as a response is observed and the patient stabilized, it is recommended that NO be reduced to 10 to 5 ppm[30].

6. Sildenafil is a selective type 5 phospho-diesterase inhibitor. Sildenafil (75 mg) decrease the pulmonary wedge pressure and reduce the PAP to a greater extent than inhaled NO (80 ppm)[1,25,30-40]. In a small case series, oral Sildenafil was given in combination with i.v. prostacyclin improved hemodynamics and symptoms in adults with pulmonary PH[1,30-32]. Inhaled Iloprost in combination with oral Sildenafil produced a greater and more prolonged fall in PAP than either agent alone[32]. Sildenafil is available as 25 mg tablets. Dosage should start at 0.1 mg/kg, increased stepwise by 0.1 mg/kg up to 0.5 mg/kg every 6 hours. However, in patients with cardiac disease, initial dosage may be as high as 0.5 mg/kg every 6 hours, with stepwise increases by 0.5 mg/kg up to 1.0–1.5 mg/kg. The i.v. dose has been started at 0.2 mg/kg/hour, although currently only available as part of clinical trials. As the effects of sildenafil are not selective to the pulmonary circulation, at higher concentrations, it may lead to a fall in systemic pressure. Furthermore, because of a longer half-life compared to NO, its effects are maintained for several hours[1].

In pediatric population, there are only case reports that demonstrate possible clinical benefits from the use of Sildenafil for PH[31,35]. A recent systematic literature review by Cochrane of four controlled clinical trials, involving 77 patients (adults and children), two of these studies assessed the short-term effects of Sildenafil, while the other two assessed the long term effects[33]. Many questions remain unanswered about the true efficacy of Sildenafil for the treatment (chronic and acute) of patients with PH, and it is necessary to define the dosage, intervals and safety for pediatric patients.

The largest study to assess the effect of Sildenafil in pediatric patients was reported by Schulze-Neick et al. The sample comprised 24 children with PH secondary to congenital heart disease. The study is controlled with inhaled NO; it assessed 12 children by cardiac catheterization and 12 by hemodynamic monitoring during the immediate postoperative period. Intravenous Sildenafil was more effective for reducing PVR than was NO. It

caused an increase in GMPc 2 to 2.4 times greater than with NO alone. The selective pulmonary vasodilator effect of Sildenafil was associated with increased intrapulmonary shunt, which was not clinically significant in this study, but could represent an undesirable effect if we consider patients in the postoperative period of congenital heart surgery[36].

The true role of this drug for patients with PH has not yet been established, but it appears to be a useful alternative for weaning from NO and during acute PH crises.

7. Endothelin antagonists: In patients with PH, endothelin-1 (ET-1) levels are elevated in plasma, and are inversely correlated with prognosis[6]. ET-1 is a powerful vasoconstrictor.

Bosentan is an oral endothelin receptor antagonist, and has a discretely greater affinity for ET-A. Its pharmacological action is by means of vasoconstriction inhibition and the action of mitogenesis and remodeling[6]. It improves symptoms and hemodynamics over 3 months but may cause significant hepatotoxicity. It has been used successfully in children. It is available as 62.5 and 125 mg tablets. It has been approved for use in adults for the treatment of primary PH. Dosage is 1–2 mg/kg every 12 hours, up to 2–4 mg/kg every 12 hours. AST enzymes should be monitored[2].

Bosentan use in pediatric is limited. Barst et al performed an open, uncontrolled study involving 19 patients originally treated at two centers (New York and Colorado). These patients had functional class II or III and weighed more than 10 kg. Thirteen percent reduction in PmAP was observed; however, no changes were observed in walking test results or functional class. Apparently, the pharmacokinetic and hemodynamic effects of Bosentan were similar to those observed in adult patients. The Food and Drug Administration (FDA) approved the drug for use with children over 12 years or with weight over 40 kg[6,41].

Rosenzweig et al performed a study involving 86 children with PH of varying etiology. They were given long-term Bosentan (14 months), in isolation or concurrently with prostacyclins. The children were evaluated in terms of hemodynamic variables and functional class (WHO classification). Int the study, there were reductions in PmAP (64±3 mmHg to 57±3 mmHg) and PVR (20±2U xm² to 15±2U xm²), and improvements in functional class in 46% of the patients[42]. The suggested dose is 62.5 mg (twice a day for the first month), followed by progressive increase until the ideal dose of 125 mg is reached (twice a day), making a total daily dose of 250 mg[42].

Other selective ET-A inhibitors, such as sitaxsentan and ambrisentan, are under investigation for use in PH. The action of these drugs 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 similar to that of Bosentan[6].

8. Prostacyclin (epoprostenol): The use of prostacyclins or prostacyclin analogues for PH treatment is based on an "imbalance" between thromboxane and prostacyclin

metabolites[18,29]. Prostacyclins induce relaxation of the respiratory vascular musculature, stimulating production of cyclic adenosine monophosphate (AMP), and inhibit respiratory muscle cell growth and platelet aggregation[18,29]. It appears that chronic patients benefit from their use due to anti-proliferative property. Used with patients with advanced disease (absence of pulmonary vascular reactivity) confirmed "rescue" effect on the pulmonary vascular endothelium restoring normal function[18].

Epoprostenol is administered intravenously and appears to be effective with patients at functional classes II to IV[6]. This drug has demonstrated good results in children with severe PH associated with congenital heart disease; patients with PH associated with HIV infection and portal hypertension[20]. However, it does not appear to influence the mortality of patients with PH secondary to collagen disorders[6,43]. It requires "fully implantable" intravenous catheter for continuous infusion. Dosage is variable, between 21±7 ng/kg/minute during the first year and 32±10 ng/kg/minute after 41 months[29]. Several adverse effects have been reported: maxillary pain, headaches, diarrhea, nausea, leg pains, rubor and risk of severe infections and sepsis[29].

Iloprost is an inhaled prostacyclin analogue. Its particle size (0.5 to 3.0 µm) guarantees its pulmonary selectivity and improved tolerance[18,20]. However, its short half-life (45 minutes) demands frequent administrations (6 to 12 times per day)[18,20]. The dose varies depending upon the response of each patient. It is administered via a special nebulizer, and the maximum daily dose is 45 mcg. A small proportion of patients appear to respond in isolation[43-47]. Randomized controlled trial study showed significant improvement of secondary end points as Quality of life Scale (p=0.026), Dyspnea Index (p=0.015), improvement in 6-minutes walk test (p=0.004), improvement in functional class (p=0.03) and improvement of hemodynamic Parameters (pulmonary vascular resistance, mean pulmonary artery pressure, and cardiac index)[44]. long term follow up study showed stabilization of pre-inhalation hemodynamics, improvement in physical capacity, improvement in survival compared to historical control, improvement in NYHA functional class (at least one class), and improvement of 6 minutes walk test for at least 10% and no deterioration or death[44].

Inhaled Iloprost proved to be effective for some children with PH in a multicenter study in 22 children, aged 4.5 to 17.7 years. Twelve cases of PH were idiopathic and 10 had CHD. Acute administration of inhaled Iloprost lowered mPAP equal to that of inhaled nitric oxide with oxygen. At 6 months, Functional Capacity improved in 35% of patients, decreased in 15%, and remained unchanged in 50%[45].

Iloprost instilled endotracheally was chosen as a last resort at treatment in a critically ill new born, who did not respond to conventional treatment, including HFOV and inhalation of NO. The use of Iloprost converted permanently the right-to-left shunting, leading to a substantial improvement in oxygenation[46].

Beraprost: Is an oral prostacyclin analogue which has about 50% of the effect of epoprostenol, with a longer half-life. Its hemodynamic effects in the long term (more than

6 months) have not yet been fully established[48,49]. This drug is not yet approved for pediatric use.

9. The combined use of drugs which have different sites of action appears to be promising for PH treatment[39-40,50-51]. Adjuvant use of Bosentan and Sildenafil with patients already on prostacyclin (oral, inhaled or intravenous) improved the variables under analysis[50,51]. A Long-term treatment with Sildenafil and Bosentan improved both exercise capacity and functional class in patients with idiopathic pulmonary arterial hypertension and in those with hypertension due to congenital heart disease. The changes were more marked in patients with idiopathic pulmonary arterial hypertension[39,40].

10. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) reflect pressure and volume loads to the pulmonary artery and right ventricle and may help to identify children with ventricular septal defect complicated by PHT that demands early intervention[52]. BNP measurements may also be used to guide therapy. There may also be therapeutic potential via recombinant BNP or neutral end peptidase inhibitors in RV dysfunction and PAH[52].

11. High frequency oscillatory ventilation (HFOV) is used in a randomized clinical trial of neonates with severe PPHN, HFOV was as effective as inhaled NO. In the presence of severe lung disease, HFOV was more effective than inhaled NO. In the absence of parenchymal lung disease, inhaled NO was more effective than HFOV. Combining inhaled NO and HFOV was more successful than either alone[53].

12. Surgical options including transplantation are indicated in **c**hildren with frequent syncope and DHF, which have poor prognosis. Effort-induced syncope occurs because of an inability to increase cardiac output to maintain cerebral blood flow. A patent foramen ovale is capable of increasing these patients' survival. Systemic arterial oxygen saturation declines, but cardiac output and oxygen supply to tissues improve, through the shunt. Despite experience with more than 100 patients with atrial septostomies for PH, the procedure is still considered investigative[54,55]. Cardiopulmonary or pulmonary, unilateral or bilateral transplantation has been indicated for patients with PH since 1981. Currently, combined transplantation is indicated only in cases of anatomical cardiac defects, with no possibility of surgical correction, since morbidity and mortality are higher. Overall surgical mortality for lung transplantation is 16 to 29%. Pediatric data from the International Society for Heart and Lung Transplantation demonstrate that 2-year survival is 65% and 5-year survival is 40%[56,57].

Transplantation is not the perfect treatment for PH; it is associated with severe post-transplantation morbidity and mortality. Currently, transplantation is recommended for a specific group of patients, who do not respond to vasodilatador therapy, or who exhibit clinical/hemodynamic deterioration during vasodilator therapy (isolated or combined drug use), Figure 1[16,57].

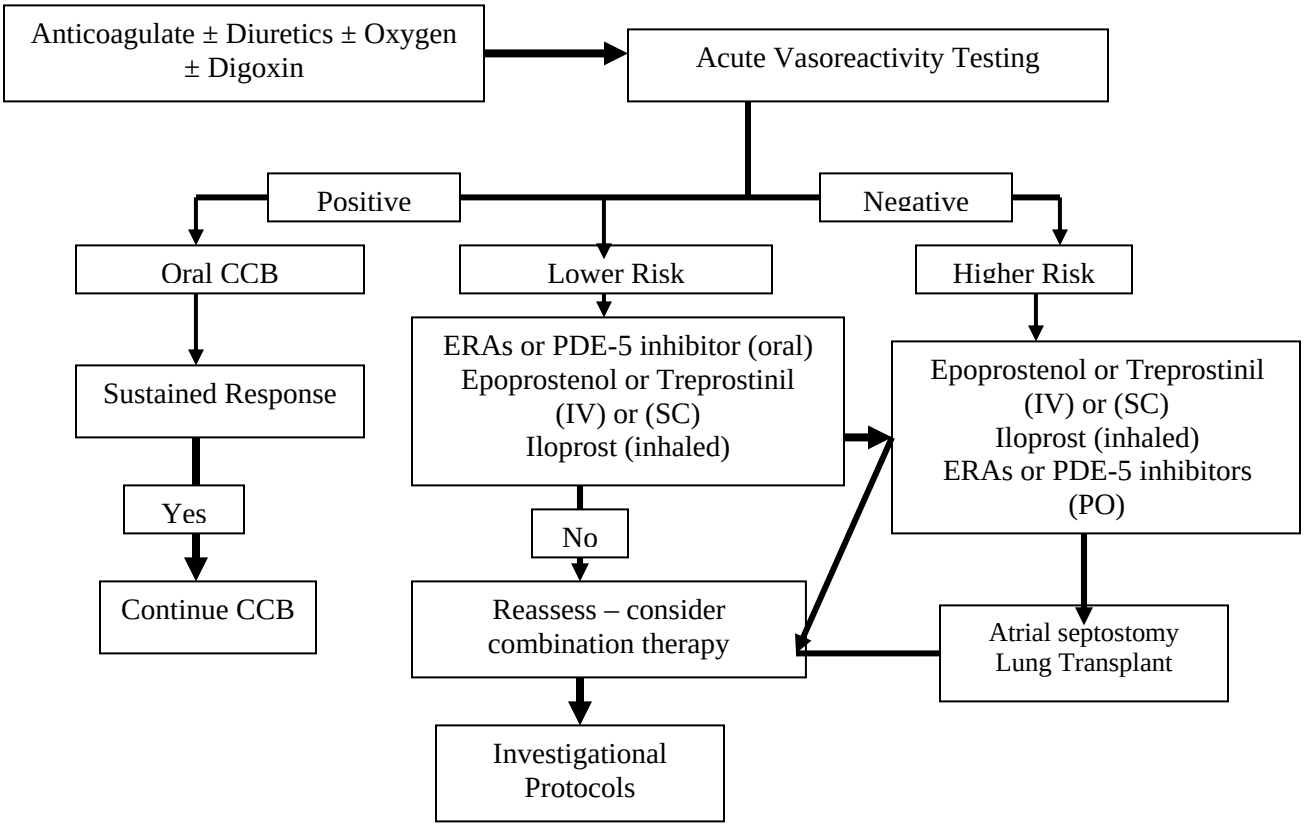

Figure 1: Strategy for Optimal Treatment

CCB: Calcium channel blocker
ERA: Endothelin receptor antagonist
PDE-5: Phosphodiesterase-5 inhibitors
IV: Intravenous
SC: Sub cutaneous

CONCLUSION

The management of PH is a challenge, even by experienced clinicians. Recent advances in understanding the pathophysiologic mechanisms involved indicate that there are differences in disease presentation in the pediatric population. New drugs have emerged and opened up fresh prospects for medium and long-term prognosis.

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