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Insight into Pulmonary Arterial Hypertension Associated with Congenital Heart Disease (PAH-CHD): Classification and Pharmacological Management from a Pediatric Cardiological Point of View

I-Chen Chen[1] and Zen-Kong Dai[1,2]

Compared with adult patients with pulmonary hypertension (PH), pulmonary vascular disease is characterized by complex heterogeneity in pediatric patients. The Nice PH classification does not completely characterize or individualize any subgroup of pediatric PH. This is in contrast to the Panama classification, in which prenatal and fetal origins of many pulmonary vascular diseases in neonates and children, perinatal pulmonary vascular maladaptation, prenatal and postnatal pulmonary vascular mal-development, and pulmonary vascular hypoplasia are included. Currently, the updated treatment algorithm for adults with pulmonary arterial hypertension (PAH), including PAH associated with congenital heart disease (PAH-CHD) and idiopathic PAH, etc. has been reported. It has been suggested to treat FC III patients with Eisenmenger syndrome (ES) with bosentan. However, there is no evidence-based treatment algorithm for children with PAH-CHD. Moreover, it is necessary to develop a more comprehensive algorithm in which multiple specific pediatric risk factors are determined, and the critical goal of treatment should be to permit normal activities without the need to self-limit in children with PAH-CHD. Together, the beneficial data on specific-target pharmacologic interventions are still quite preliminary, and large trials are warranted. Specifically, the extrapolation of the other forms of the disease, such as ES, should be undertaken carefully.

Key Words: Congenital heart disease • Eisenmenger syndrome • Pulmonary arterial hypertension • Target therapy

INTRODUCTION

Pulmonary circulation is characterized by low-resistance and high compliance. By definition, pulmonary hypertension (PH) is the mean pulmonary arterial pressure of more than and/or equal to 25 mmHg in patients with various disorders, including cardiac, pulmonary parenchymal and pulmonary venous disorders. Furthermore, PH could result from increases in pulmonary flow volume, pulmonary vascular resistance or pulmonary venous pressure. With progressive increases in pulmonary vascular resistance, PH subsequently leads to right ventricular failure and even mortality. Pulmonary arterial hypertension (PAH) is a clinical condition characterized by the presence of pre-capillary PH in the absence of other causes,[1] and is divided into idiopathic PAH (IPAH)

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[1]Department of Pediatrics, Division of Pediatric Cardiology and Pulmonology, Kaohsiung Medical University Hospital, Kaohsiung Medical University; [2]Department of Pediatrics, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.
Address correspondence and reprint requests to: Dr. Zen-Kong Dai, Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, No. 100, Shih-Chuan 1st Road, Kaohsiung, Taiwan. Tel: 886-7-312-1101 ext. 6507; Fax: 886-7-320-8316; E-mail: zenkong@kmu.edu.tw

and associated PAH. Currently, the modified PH classification (Table 1)[2] was proposed at the 5th World Symposium on Pulmonary Hypertension (WSPH) in Nice, France. Based on human and animal studies, pulmonary arteriolar remodeling, inflammation, thrombosis *in situ*, dysfunction of underlying cellular pathways and increased vascular tone are related to the development of PH. In addition, advanced research has suggested that the quasi-neoplastic in endothelial cell growth[3,4] and 'Seed and Soil'[5-7] hypotheses could be explained by the pathogenesis in PAH.

It is reported that the increased vascular tone results from an imbalance between vasodilators and vasoconstrictors, so-called pulmonary endothelial dysfunction, in PH. The pulmonary arteriolar remodeling is characterized by medial hypertrophy with reversibility in the early phase, and by the formation of complex cellular fibrosis and neointimal plexiform lesions with irreversibility in the advanced phase, respectively.[8,9] Currently, the key target of therapy is "to reverse the remodeling" and

Table 1. Updated clinical classification of pulmonary hypertension (From the 5th World Symposium on Pulmonary Hypertension in Nice, 2013)

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic PAH
   1.2. Heritable
      1.2.1. BMPR2
      1.2.2. ALK1, ENG, SMAD9, CAV1, KCNK3
      1.2.3. Unknown
   1.3. Drug- and toxin-induced
   1.4. Associated with
      1.4.1. Connective tissue diseases
      1.4.2. HIV infection
      1.4.3. Portal hypertension
      1.4.4. Congenital heart diseases
      1.4.5. Schistosomiasis

1' Pulmonary Venous Occlusive Disease and/or Pulmonary capillary hemangiomatosis

1" Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension owing to left heart disease
   2.1. Left ventricular systolic dysfunction
   2.2. Left ventricular diastolic dysfunction
   2.3. Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction

3. Pulmonary hypertension owing to lung diseases and/or hypoxia
   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 (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1. Hematologic disorders: chronic hemolytic anemias, 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

ALK1, activin-like receptor kinase-1; BMPR2, bone morphogenic protein receptor type II; CAV1, caveolin-1; ENG, endoglin; KCNK3, a gene encoding potassium channel super family K member-3; SMAD9, mothers against decapentaplegic 9.

correct the imbalance of vascular tone.

It is extremely important as to whether some patients are diagnosed very early, before remodeling occurred, or whether they represent a different phenotype in congenital heart disease (CHD). Therefore, it is necessary to characterize the pulmonary vessel phenotypes to determine the reversibility of vascular remodeling in PAH, and to recognize the ideal treatment goal in PAH to be the dis-obliteration or reopening of occluded small pulmonary arterioles.

PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE (PAH-CHD)

Compared with adult patients with PH, pulmonary vascular disease is characterized by complex heterogeneity in pediatric patients. A revised classification of pediatric pulmonary vascular disease had been newly reported by some authors[10] (Table 2), in which pediatric PH can be involved in the prenatal and fetal origins of many pulmonary vascular diseases in neonates and children, perinatal pulmonary vascular maladaptation, prenatal and postnatal pulmonary vascular mal-development, and pulmonary vascular hypoplasia (Table 3). In the Nice PH classification, PH can be noted in congenital heart diseases in 1.4.4, congenital left heart inflow/outflow tract obstruction in 2.4, and segmental PH in 5.4, respectively. In general, except that of left heart disease, PH patients with CHD are recognized as PAH-CHD.

Accordingly, CHD is common, with an estimated incidence of 1% globally. Because of the typical lifelong course of the disease, continuity of care beyond childhood is paramount for CHD patients. Current advances in pediatric cardiology and surgery have led to many more pediatric patients with CHD surviving into adulthood. In the other words, a wide spectrum of cardiac defects can be associated with pulmonary arterial hypertension, resulting in severe functional impairment, affecting both the patients' survival and quality of life.

Table 3. Classification of pediatric pulmonary hypertensive vascular disease (Pediatric PH category 1 to 2 adapted in ref. 10)

Category 1. Prenatal/developmental pulmonary vascular disease
1.3. Associated with fetal cardiac maldevelopment
1.3.1. Premature closure of foramen ovale or ductus arteriosus
Idiopathic
Drug induced
1.3.2. Congential heart defects associated with PVD in the fetus
Transposition of the Great arterial with IVS
Hypoplastic left heart syndrome with intact atrial septum
Obstructed total anomalous pulmonary venous connection
Common pulmonary vein atresia
Category 2. Perinatal Pulmonary Vascular Maladaptation
2.1. Idiopathic Persistent Pulmonary Hypertension of the Newborn (PPHN)
PPHN associated with or triggered by
– Sepsis
– Meconium aspiration
– Congenital heart disease
– Congenital diaphragmatic hernia
– Trisomy 21, 18, 13
– Drugs: Diazoxide
– Hypobaric, hypoxic exposure

IVS, intact ventricular septum; PVD, pulmonary vascular disease.

Table 2. The broad schema of 10 basic categories of pediatric pulmonary hypertensive vascular disease (adapted in ref. 10)

1. Prenatal or developmental pulmonary hypertensive vascular disease
2. Perinatal pulmonary vascular maladaptation
3. Pediatric heart disease
4. Bronchopulmonarydysplasia
5. Isolated pediatric pulmonary arterial hypertension
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7. Pediatric lung diseases
8. Pediatric thromboembolic disease
9. Pediatric hypobaric hypoxic exposure
10. Pediatric pulmonary vascular disease associated with other system disorders

In the Nice PH classification, it had been suggested that PAH-CHD in adults should be aligned with the pediatric classification. In statistics, PAH is found in about 5-10% of adults with CHD,[11] and the demographics of CHD patients are changing.[12] Quite importantly, the development of PAH in adults with CHD is associated with more than twice the risk of mortality and three times the rate of morbid complications noted.[13] Furthermore, the PAH-CHD could be divided into five individual groups as follows:

I. The left to right shunt CHD

The patients with left to right shunt could be further divided into correctable and non-correctable groups. Their moderate to large defects could result in mildly to moderately increased pulmonary vascular resistance.

II. Eisenmenger syndrome

In 2% of the hospital cohort, the reverse shunt develops and was specified as advanced and terminal stage of a spectrum of structure and functional changes in the pulmonary vasculature, which leads to progressive increases in pulmonary vascular resistance called Eisenmenger syndrome (ES). Very importantly, it is reported that its prognosis is poor and functional impairment is underestimated in ES.[14,15] This is because the exercise limitation is present from childhood, resulting in chronic adaptation of everyday activities to a lower intensity. Again, a recently modified consensus for the definition for Eisenmenger syndrome has been developed, where ES further includes the following:

(1) Patients with CHD characterized by left to right shunt.
(2) Patients with advanced pulmonary vascular disease early in life, and have never presented with increased pulmonary flow.
(3) Patients with cyanotic congenital cardiac defects associated with exceedingly high pulmonary vascular resistance, i.e. transposition of the great arteries (TGA). It was reported that ES had been reported in 50% and 10% of patients with large unrepaired ventricular septal defect and atrial septal defect, respectively, and all patients with unrepaired truncus arteriosus are at risk of developing ES. Therefore, the associated defect of ES is a critical determinant of its dependent prognostic implication. Subsequently, patients with ES have reduced life expectancy, even if many survive into their third or fourth decade. However, defect closure is contraindicated. The key to the relative longevity of these complex CHD patients lies in the unique adaptation of the right ventricle.

III. PAH with coincidental CHD

Found in CHD patients with marked elevation in pulmonary vascular resistance (PVR) in the presence of small cardiac defect which is out of proportion explained for the development of PAH. The screening for the mutation in a German cohort study revealed that there were two PAH-related mutations noted (18%) in CHD-PAH patients, compared with 27.5% of idiopathic pulmonary hypertension.[16] This inferred that there should be some other risk factors, such as epigenic factors and gene defects, instead of small cardiac defects, that lead to the development of PAH.

IV. Post-operative PAH

In some cases of CHD after repair, the increased pulmonary artery pressure with more than 3 WUm^2 of pulmonary vascular resistance index (PVRI) persists immediately after surgery or recurs /develops months or years after surgery in the absence of significant post-operative hemodynamic lesions. Together, the operation includes arterial or atrial switch operation for TGA with intact ventricular septum (TGA/IVS) and the repair of left heart obstruction, Tetralogy of Fallot, pulmonary atresia with ventricular septal defect, multiple aorta-pulmonary collateral arteries (MAPCAs) and aortopulmonary shunt.

V. Pulmonary vascular disease following staged surgery for single ventricle

The pulmonary vascular disease could be noted in patients undergoing the following operations:

(1) Stage 1 operation, including main pulmonary artery (MPA) or branch pulmonary artery (PA) banding, modified Norwood, hybrid procedure, surgical aorta/ventricular to pulmonary shunt, and patent ductus arteriosus stenting.
(2) Superior vena cava to PA anastomosis (Glenn shunt).
(3) Total cavopulmonary anastomosis (Fontan-type operation), in which there is increased pulmonary vascular resistance without elevated pulmonary artery pressure noted. The underlying mechanism behind increased PVR is unclear and likely to be multifactorial,

but possible causes include non-pulsatile blood flow through the pulmonary arteries and endothelial dysfunction.[17,18]

Currently, in either pediatric or adult patients with PAH-CHD for whom operation in not an option, instead of traditional therapy, advanced therapy (AT) targeting pulmonary vascular remodeling and abnormal vascular tone probably can provide a beneficial treatment option.

RESOLVING THERAPY STRATEGY FOR PAH-CHD

Prior to 1995, the traditional therapies for adults with PAH-CHD, including ES, were limited. These therapies have included oxygen, warfarin, diuretics, calcium channel blocker, antiarrythmics, anticoagulants, and iron supplementation. In addition, until recently, options included palliative therapies or lung/heart-lung transplantation in children and adult patients with PAH, especially IPAH and PAH-CHD, and the latter is for small highly-selected subgroups.[19] However, all of the traditional therapies do not seem to improve survival rates.[20,21] The benefit of supplemental oxygen administration is not approved, given the conflict between recognized concomitant oxygen-responsive and unresponsive components to hypoxemia in many adults with PAH-CHD and the lack of sufficient therapeutic effects to assess benefit.[21,22]

In adults with Eisenmenger physiology, recognition of *in vivo* pulmonary thrombus,[23] in contrast with reports of *in vitro* abnormalities of coagulation in persons with cyanosis,[23] has led to a debate over the potential benefit of oral anticoagulant therapy, particularly with the concomitant bleeding diathesis inherent in the condition. In patients with active or chronic hemoptysis, anticoagulation is contraindicated.

Recently, accompanied by the development of modern molecular biology, three classes of pulmonary vasodilators have emerged as so-called AT for PAH, including endothelin receptor antagonist (ERA), prostaglandin derivative (PG) and phosphodiesterase-5 inhibitor (PDE5i). Together, epoprostenol, bosentan, treprostinil, iloprost, sildenafil and ambisentan have been successively developed during the decade with varied classes of recommendation and evidence for PAH (Table 4).

Currently, the AT can improve exercise capacity, hemodynamic parameters, functional class, quality of life and survival in adults with PAH, especially IPAH, connective tissue disease (CTD-APAH) or anorexigen-APAH. Therein, some patients with IPAH had been treated successfully with vasodilators with normal or subnormal hemodynamic statuses. The efficacy of AT in adults with PAH and the poor prognosis with traditional therapies have resulted in the inclusion of these new agents in the current recommendations in pediatric patients with PAH.

Pediatric PAH treatment goals may be divided into patients at lower risk or higher risk of death (Table 5). As in adults, clinical evidence of right ventricular failure, progression of symptoms, World Health Organization functional class III-IV, and elevated brain natriuretic peptide levels are recognized as creating a higher risk of death. Also, abnormal hemodynamics can be related to a higher risk as well. Together, the related parameters include the ratio of mean pulmonary artery pressure (PAPm) to systemic artery pressure, a right atrial pressure of more than 10 mm Hg, and a PVRI of greater than 20 Wood units $\times$ m^2 in cardiac catheterization. But, the value noted to be associated with higher risk is quite different than those for adult patients.

In the beginning of developing the algorithm in the treatment for pediatric PAH, some challenges have been raised. First, there is less evidence of treatment efficacy in children than in adults. Second, the functional class stratification alone in current form which delineates treatment course is not sufficient for children of all ages. Finally, adult recommendations do not consider

Table 4. Targeted therapy for adult and pediatric PAH (modified from ref. 21, 27)

	Adult	Pediatrics
CCB	I-C	I-C
IV epoprosternol	I-A	I-B
SQ treprostinil	I-B (FC III), Iia (FC IV)	IIa-C
IV treporstinil	IIa (FC III, IV)	IIa-C
Ambrisentan	I-A (FC II, III)	IIa-C
Bostentan	I-A (FC II, III)	I-B
Sildenafil	I-A (FC II, III)	I-B (US?)
Tradlafil	I-B (FC II, III)	IIb-C
Inhaled iloprost	I-A (FC III), IIaC (FC IV)	IIb-C
Inhaled trepostinil	n/a	IIb-C

CCB, calcium channel blocker; IV, intravenous; SQ, subcutaneous.

the different inherence in common etiologies, natural history and treatment goals for children with PAH. Moreover, it is necessary to develop a more comprehensive algorithm in which multiple specific pediatric risk factors are considered, and the critical goal of treatment should be to permit normal activities without the need to self-limit, such as functional class (FC) I or II.

In children with a positive acute vasoreactivity testing (AVT), oral calcium channel blockers (CCBs) may be initiated (Figure 1). However, because of the negative

Table 5. Pediatric determinants of risk for PAH (modified from ref. 24)

Lower risk	Determinant of risk	Higher risk
NO	Clinical evidence of RV failure	Yes
NO	Progression of symptoms	Yes
NO	Syncope	
	Growth	Failure to thrive
I, II	WHO Functional Class	III, IV
Minimally elevated	BNP/NTproBNP	Significantly elevated rising level
	Echocardiography	Severely RV enlargement/dysfunction
		Pericardium effusion
Systemic CI > 3.0 L/min/m^2	Hemodynamics	Systemic CI < 2.5 L/min/m^2
MPAP/mSPAP < 0.75		MPAP/mSPAP > 0.75
Acute vasoactivity		RAP > 10 mmHg
		PVRI > 20 WU × m^2

BNP, B-type natriuretic peptite; MPAP, mean pulmonary artery pressure; mSPAP, mean systolic pulmonary artery pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; RV, right ventricle.

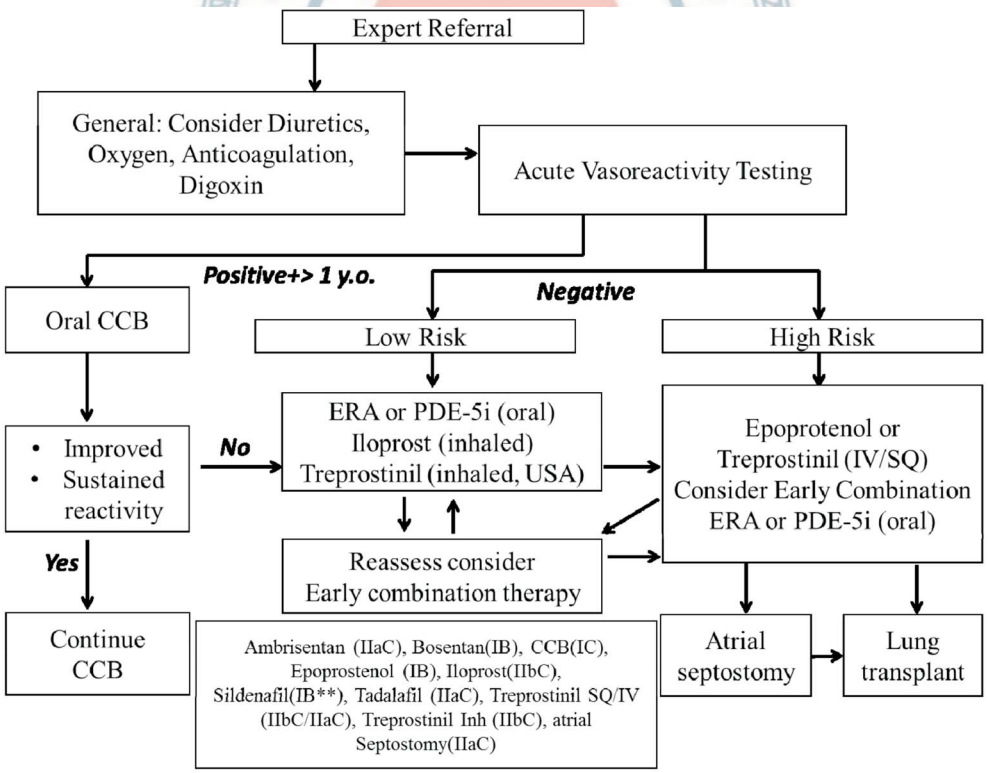

Figure 1. *Consensus pediatric IPAH/FPAH treatment algorithm.[24] CCB, calcium channel blocker; ERA, endothelin receptor antagonists; IPAH/FPAH, idiopathic pulmonary arterial hypertension/familial pulmonary arterial hypertension; IV/SQ, intravenous/subcutaneous; PDE-5i, phosphodiesterase-5 inhibitors.*

inotropic effects noted in young infants, CCBs should be avoided until the child is older than one year of age. For children with a negative AVT response or in children with a failed or non-sustained response to CCBs, risk assessment should determine additional therapy (Table 5). Since the specific number of lower- or higher-risk criteria to drive therapeutic choices is not yet known, either risk criteria should be considered as justification for AT in children with IPAH/familial pulmonary arterial hypertension (FPAH). In children with a negative AVT and lower risk, oral monotherapy with endothelin receptor antagonists (bosentan,[25,26] ambrisentan[27,28]) and PDE5 inhibitors (sildenafil,[29,30] tadalafil[31,32]) or PG (iloprost,[33] treprostinil[34]) is recommended to be initiated.

THE EVIDENCE-BASED ADVANCED PHARMACOLOGIC THERAPY FOR PAH-CHD

The rationale for treatment is clear, given the progressive character of PAH-CHD. Currently, the updated treatment algorithm for adults with pulmonary arterial hypertension has been reported, which includes PAH-CHD, IPAH, heritable pulmonary artery hypertension and PAH associated with connective tissue disease, etc (Table 6).[1,35] And, it is suggested that FC III patients with ES should be treated with bosentan. However, there is no evidence-based treatment algorithm for children with PAH-CHD. In fact, PAH-CHD has been recognized as potentially being different from IPAH or other APAH.

Regarding the effectiveness of such treatments as noted in current studies, bosentan treatment has been shown to improve short-term exercise tolerance in adult patients with PAH-CHD in functional classes II, III and IV.[36] Recently, the beneficial data on specific-target pharmacologic interventions in CHD with significant PAH are still quite preliminary, and large trials are warranted. Specifically, the extrapolation of other forms of the disease, such as ES, should be made carefully.

Some of the AT agents (e.g., intravenous prostacyclin and oral sildenafil) have yielded improvements in hemodynamics, exercise tolerance, and/or systemic arterial oxygen saturation in limited case studies with PAH-CHD.[37-43] The BREATH-5 study demonstrated that bosentan-treated adult patients with functional class III ES improved significantly in contrast to untreated patients.[44] In addition, it was reported that AT for adults with ES in a contemporary cohort was associated with a lower risk of death among a total of 68 patients who started with bosentan (73.5%), sildernafil (25%) and epostrostenol (1.5%).[14]

The potential for significant adverse reaction due to these agents has been recognized. Moreover, there is less available data regarding combination therapy to be able to make a detailed recommendation for PAH-CHD in children. The theoretical possibility of worsening the right-to-left shunting raises questions about the safety of using pulmonary artery modulating therapies that also have the potential for systemic vasodilatation.

CONCLUSIONS

Many therapies for PAH have been approved re-

Table 6. Recommendations for PAH associated with congenital cardiac shunt (modified from ref. 37, 38)

Statement	Class	Level
The ERA bosentan is indicated in FC III patients with ES	I	B
Other ERAs, PDE-5i & prostanoids should be considered in ES patients	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
Use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial O_2 saturation & reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is > 65%	IIa	C
Combination therapy may be considered in patients with ES	IIb	C
Use of CCBs is not recommended in patients with ES	III	C

CCBs, calcium channel blockers; ERA, endothelin receptor antagonists; ES, Eisenmenger syndrome; FC, functional class; PA, pulmonary hypertension; PDE-5I, phosphodiesterase-5 inhibitors.

cently, but none has been shown to improve the pulmonary vascular obstruction or to cure the disease in any patient. Although pulmonary vascular remodeling is similar in pediatric PH, there are more complex and heterogeneous etiologies, compared with adult PH. There is a need for concern regarding the pulmonary vasculature of prenatal mal-development and perinatal mal-adaptation in assessing the efficacy of AT for pediatric PH.

The Nice PH classification, however, does not completely characterize or individualize any subgroup of pediatric PH, in contrast to the Panama classification. Therefore, it is inferred that serial re-assessment of responses to the targeted PAH agents remains a critical part of the long-term care of children with PAH-CHD. In addition, the implementation of guidelines specific to pediatric PAH, such as IPAH and FPAH, is a useful tool for the management of this PAH-CHD, as targeted treatment goals are not always the same as they are in adults with PAH-CHD. Future clinical trials designed specifically for children and adults with PAH-CHD are essential to further optimize therapeutic guidelines.

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