Adult Congenital Heart Disease and Pulmonary Arterial Hypertension: The Texas Adult Congenital Heart Program Experience

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Abstract: Congenital heart disease (CHD) is a common structural defect of the heart or major blood vessels. Patients with adult congenital heart disease (ACHD) have medical needs that are distinct from those of pediatric patients with CHD, and the transition into adult health care is important for management of the patient with ACHD. A large proportion of patients with CHD develop diseases and complications associated with the long-term stress of intracardiac shunts. Pulmonary arterial hypertension (PAH) is a significant complication of some CHD lesions. The treatment of these patients remains challenging due to their combined heart and lung disease, and multidisciplinary care is ofen necessitated for a variety of secondary conditions. A number of treatment options are available for the management of PAH associated with CHD, including prostanoids, phosphodiesterase type-5 inhibitors, and endothelin receptor antagonists. This article discusses the diagnosis and management of such ACHD patients with PAH.

Keywords: congenital heart disease; echocardiography; endothelin receptor antagonist; heart failure; phosphodiesterase type-5 inhibitor; prostacyclin; pulmonary arterial hypertension

Introduction

Pulmonary arterial hypertension (PAH), classified as group 1 pulmonary hypertension, is a progressive disease characterized by an increase in pressure in the small pulmonary arteries that leads to elevated vascular resistance, right ventricular failure, and death. Pulmonary arterial hypertension is defined as a resting mean pulmonary artery pressure (PAP) $\geq$ 25 mm Hg with a pulmonary capillary wedge pressure $\leq$ 15 mm Hg based on right heart catheterization (RHC) (some definitions also require pulmonary vascular resistance [PVR] of $>$ 3 Wood units).[1–4] Conditions that may lead to the development of PAH are diverse and include idiopathic PAH (IPAH), for which no specific cause has been identified; heritable PAH (formerly classified as familial PAH), which has a genetic component and thus presents with increased frequency in families; and PAH associated with other conditions (APAH), including portopulmonary hypertension, connective tissue disease, and congenital heart disease (CHD).[5] In patients with CHD associated with PAH (CHD-APAH), targeted medical therapies, including prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase type-5 (PDE-5) inhibitors, have demonstrated beneficial effects on exercise capacity and hemodynamics; however, the long-term efficacy of such treatments remains inconclusive.[2]

Congenital heart disease results from congenital structural defects of the heart or major blood vessels. The incidence of CHD is approximately 8 per 1000 live births, and studies show that 2 to 3 out of 1000 infants require invasive treatment for life-threatening defects during the first year of life.[6] The American College of Cardiology's

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(ACC) 32nd Bethesda Conference in 2001 and recent literature estimate that 1.3 million patients with adult CHD (ACHD) are alive in the United States today.[7] Within the next decade, 1 in 150 young adults may have some form of CHD.[8] The death rate in 2005 for those patients with CHD with the most complex defects was 1.2 per a population of 100 000.[6] It is important to note that reliable estimates are only available for those patients with the most severe defects, as mild defects can remain undetected until adulthood.

Improvements in pediatric cardiovascular care have increased the survival rate of infants with CHD; currently, 85% of babies born with CHD will survive into adult life.[8] It is increasingly common for adult cardiologists to encounter patients with ACHD in their clinical practice.[9] Care of the patient with ACHD remains challenging because these patients usually fall into 2 categories: 1) adults with newly diagnosed CHD, and 2) adults who underwent palliation or repair during childhood. Both of these patient groups offer a specific difficulty for the clinician because the symptomatology may be variable, and accurate medical and surgical history may be difficult to obtain. In addition, many patients with ACHD are at risk for PAH and should be evaluated accordingly.[10]

Patients with ACHD are at an increased risk of mortality compared with the general population.[11] A recent study compared the Dutch Congenital Corvitia (CONCOR) registry database for ACHD with the national Dutch mortality registry. In that study, mortality, cause of death, and cardiovascular complications were analyzed in patients with CHD.[11] Increased mortality was noted in patients with CHD as compared with the general population in a bimodal distribution (patients aged $>$ 60 years and $<$ 5 years). The majority of deaths (77%) were attributed to cardiovascular complications (77%), chronic heart failure (26%), and sudden death (19%).[11]

One of the most serious cardiovascular complications of CHD is the development of PAH, which is often caused by the effects on the pulmonary vasculature of a chronic left-to-right cardiac shunt.[8,12] The purpose of this article is to discuss the diagnosis and treatment of PAH in patients with ACHD, using both clinical studies and the expertise of the multidisciplinary team at our ACHD program, the Texas Adult Congenital Heart (TACH) Program (Houston, TX).

CHD Lesions and the Development of PAH

Several malformations of the heart lead to CHD. Table 1 lists these malformations, their overall prevalence in patients with CHD, survival outcomes, and common complications. The different malformations that cause CHD can be classified into 3 broad categories: shunt lesions, obstructive lesions, and complex CHD, which often combines both shunt and obstructive lesions.[10,13,14] Shunt lesions may be left-to-right, leading to increased pulmonary blood flow and pulmonary overcirculation; right-to-left, where deoxygenated blood flows into the aorta after bypassing the lungs; and/or bidirectional, where blood flows both left-to-right and right-to-left during ventricular systole.[14] Obstructive lesions involve narrowing of 1 or both ventricular outflow tracts, semi-lunar valves, and/or great arteries, causing increased ventricular afterload.[13] This severe stenosis results in increased hemodynamic pressure gradients. Complex CHD shows great heterogeneity and often involves combinations of the above lesions, frequently with valve and/or chamber hypoplasia or atresia, and it usually requires surgical palliation for the patient to reach adulthood.[10]

Prognostic indicators for the development of PAH in ACHD include the type and size of the defect; the magnitude of shunt flow (ratio of pulmonary blood flow to systemic blood flow); the presence of surgical repair, including correction, palliation, and age of the patient at repair; and the age of the patient.[15,16] All 3 types of the aforementioned CHD scenarios lead to pathophysiological states, which are characterized by hemodynamic changes of both the cardiac and pulmonary vascular systems,[17] and that can lead to the development of PAH, even in patients who have undergone shunt repair at a young age. Many cases of PAH develop in patients with large systemic-to-pulmonary shunts. In such patients, the excess pulmonary blood flow leads to an increase in PAP, progressive pulmonary vasculature injury, and an increase in PVR.[12] Cardiac defects with higher PAP and PVR values have been associated with an increased prevalence of PAH.[18]

The most severe form of CHD-APAH, Eisenmenger's syndrome (ES), can occur when changes in the pulmonary arteries result in PVR that exceeds systemic vascular resistance, leading to increased pressure in the right side of the heart and resultant reversal of left-to-right to right-to-left or bidirectional shunt flow. In particular, patients with an unrepaired large ventricular septal defect, atrial septal defect, atrioventricular canal, and/or a patent ductus arteriosus are likely to develop ES.[8,19] Features that distinguish IPAH and ES are highlighted in Table 2. Specifically, patients with CHD with ES may present with hemoptysis, cerebrovascular accident, brain abscess, secondary erythrocytosis, coagulation abnormalities, cardiac arrhythmia, and even sudden death,[19] but they often have a more favorable

Table 1. Congenital Heart Lesions

Lesion	Prevalence in 2002 (%)[6,48]	Outcomes and Complications
Atrial septal defect (ASD)	18.8	Outcomes: • ASD closure before age 25 years: normal survival rate • Closure > 25 years or elevated PAP before closure: lower long-term survival rate • Benefits if closure > 40 years, but risk of atrial arrhythmia remains high Complications: • Arrhythmias; right heart failure; impaired functional capacity; **PAH and ES**; embolic cerebrovascular events
Ventricular septal defect (VSD)	20.1	Outcomes: • Unoperated patient with small restricted VSD and normal PVR: excellent; survival rate decreases with increasing size of VSD • Operated patient without PAH: normal life expectancy; operated patient with late repair and PAH: decreased survival rate Complications: • Endocarditis; arrhythmias; AS; **PAH and ES**; heart failure
Atrioventricular (AV) canal defect (endocardial cushion defect or AV septal defect)	3.1	Outcomes: • Unoperated patients with complete AV canal have 4% survival beyond age 5 years; unoperated patients with ostium primum have 50% mortality before age 20 years • Operated patients with complete AV canal have an 83% 10-year survival rate; operated patients with ostium primum have a 76% 40-year survival rate Complications: • Left AVV regurgitation; LV outflow tract obstruction; **PAH**; late-onset complete heart block; pulmonary vascular disease; atrial or ventricular dysrhythmias; left AVV stenosis; right AVV stenosis/regurgitation; residual VSD; aortic incompetence
Dextro-transposition of great arteries (TGA)	2.6	Outcomes: • Unoperated patients have 90% mortality in infancy • Operated patients with atrial switch repair have a 75%–90% 25-year survival rate, less if VSD present and with Mustard procedure • Operated patients with arterial switch repair have an 88% 15-year survival rate, less if associated with other lesions Complications: • Tachyarrhythmias; bradyarrhythmias; sudden death (7%–15%); systemic ventricular dysfunction; tricuspid regurgitation; baffle obstruction or leak; **PAH**; PA stenosis; dilation of the neoaortic root ± AR; coronary ostia stenosis
Patent ductus arteriosus (PDA)	14.2	Complications: • CHF; **PAH**; pulmonary vascular disease; endarteritis; aneurysm of the ductus arteriosus
Tetralogy of Fallot	6.1	Outcomes: • Unoperated patients have 25% mortality in first year of life, 70% before age10 years • Operated patients have 85% survival rate at age 36 years, though older age at repair decreases survival Complications: • Residual PR; residual RVOT obstruction; RV dysfunction/RVOT aneurysm; LV dysfunction; AR ± aortic root dilatation; endocarditis; atrial tachyarrhythmia; sustained VT/sudden death; heart block
Congenitally corrected TGA		Outcomes: • 25% of unoperated patients develop CHF by age 45 years; 67% develop CHF if they have associated lesions • Conventional repaired patients have a 54%–83% 10-year survival rate; double-switch repair patients do not have long-term survival rates available Complications: • RV dysfunction + CHF; TR; heart block; arrhythmias; sudden cardiac death
Single ventricles and the Fontan circulation	0.8	Outcomes: • 81% of patients who undergo Fontan operation have survival at age10 years Complications: • Atrial reentry tachycardia; thromboembolic events; RA dilatation + hepatic dysfunction; protein losing enteropathy; ventricular outflow obstruction; pulmonary arteriovenous malformations; obstruction of pulmonary veins; narrowing ± leaks in Fontan pathway; myocardial dysfunction and failure; systemic venous collateralization; sinus node dysfunction; plastic bronchitis; cyanosis

(*Continued*)

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Table 1. (*Continued*)

Lesion	Prevalence in 2002 (%)[6,48]	Outcomes and Complications
Congenital AS/bicuspid aortic valve	5.4; does not include bicuspid aortic valve	Outcomes: • Symptomatic unoperated patients have a 15%–50% 5-year survival rate, whereas asymptomatic patients have 0.4%/year average risk of sudden death • Patients who underwent operations have an 85% 25-year survival rate if underwent in childhood; if patients had post-surgical valvotomy, 40% will require reoperation within 25 years; adult post-AVR survival > 80% at 3 years Complications: • Endocarditis; recurrent AS after surgical or balloon intervention/AR; aortic root dilatation or dissection; LV dysfunction; sudden cardiac death; prosthetic complications
Coarctation of the aorta	7.6	Outcomes: • Unoperated patients have a 60%–90% mortality during the first year of life • Operated patients experience an 84% 20-year survival rate Complications (operated patients): • Persistent high blood pressure; aortic aneurysm; recoarctation or residual stenosis; coronary artery disease; AS/AR; mitral valve defects; endocarditis/endarteritis; rupture of aortic or cerebral aneurysm
Ebstein anomaly of the tricuspid valve		Outcomes: • Severe cases diagnosed in utero or as neonate have 33% mortality rate before age 10 years; live-born patients have a 59% 10-year survival rate Complications: • Arrhythmias; heart failure; cyanosis; paradoxical embolus; endocarditis; sudden cardiac death
Pulmonary stenosis	13.5	Outcomes: • Operated patients have good prognosis and normal life expectancy Complications: • Complications in unoperated patients include RV hypertrophy and RV heart failure; atrial fibrillation or flutter; endocarditis • Complications after pulmonary valvotomy include PR ± RV dilatation; residual or recurrent PS; supraventricular or ventricular arrhythmias; sudden cardiac death

Those lesions with a propensity to develop PAH are bolded.
Adapted from *Br Med Bull* with permission by Oxford University Press.[17]
Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; AVV, AV valve; CHF, congestive heart failure; ES, Eisenmenger's syndrome; LV, left ventricle; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PR, pulmonary regurgitation; PS, pulmonary stenosis; PVR, pulmonary valve replacement; RA, right atrium; RV, right ventricle; RVOT, RV outflow tract; TR, tricuspid regurgitation; VT, ventricular tachycardia.

hemodynamic profile and survival compared with patients with IPAH.[20] These favorable characteristics in patients with CHD with ES may be due to their maintenance of cardiac output, their tolerance for severe chronic cyanosis, and the indolent, progressive development of their disease state over many years.

PAH Prevalence in Patients with CHD

Several studies show that the prevalence of PAH in patients with ACHD (both in unrepaired and post-surgical patients) ranges from 4.2% to 28%.[12,16,21–25] Despite similar proportions of men and women with CHD, women are more likely to develop PAH, demonstrating a 33% higher risk compared with men.[22] This increased risk in women is consistent with the demographic data reported for other subtypes of PAH.[26–28] Eisenmenger's syndrome develops in 3.5% to 7.1% of patients with CHD with PAH.[19]

Improvements in cardiac surgery have increased the number of successful repairs of CHD lesions, the complexity of lesions that may be repaired, and the postoperative survival of patients with CHD.[29] Up to 80% of all patients with CHD undergo some surgical or percutaneous treatment of their lesion, with 40% of patients being operated on during their first year of life. Despite the increasing number of surgical repairs of CHD, the effect of lesion repair on the prevalence of PAH in patients with CHD has not been thoroughly investigated. The characteristics of PAH in patients with CHD with complete lesion repair versus patients with unrepaired or partially repaired lesions has been investigated in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL).[30] In this registry, however, "complete lesion repair" referred to those patients who completed the final repair for their lesion, even if the operation was palliative. Among the enrolled patients with CHD-APAH, the New York Heart Association (NYHA) functional class (FC) of patients with CHD with complete repair (n = 92) was superior to that of patients with CHD with unrepaired or partially repaired lesions at PAH diagnosis (n = 237; $P = 0.006$); however,

Table 2. Differences Between IPAH and ES

	IPAH	ES
Right ventricular response		
Right ventricular dimensions	Dilatation	Typically hypertrophy in post-tricuspid defects
Right ventricular functions	Rapid deterioration	Often preserved (VSD), quite stable
Cardiac output	Reduced	Sustained by R-L shunting
Prognosis	Poor; survival limited to few years after diagnosis	Not as poor; patients survive decades after diagnosis
Cyanosis		
Prevalence	When low cardiac output ± presence of PFO/ASD	Definite in ES
Severity	Rarely severe at rest	Often severe at rest, even in stable patients
Hematologic effect	Rare unstudied hematologic manifestations	Secondary erythrocytosis common in ES
Systemic complications	Not common	Common (renal dysfunction)
Associated genetic/chromosomal disorders	No	Common (Down's syndrome)
Perception of limitation	Normal perception of limitation	Known to underestimate the degree of limitation as symptoms/limitations present from childhood
Coexisting left-sided/valve disease	Rare until functional tricuspid regurgitation develops	Common (eg, AVSD, univentricular circulation)
Transplantation	Rapid progression; likely to benefit from transplantation	Slow progression; common systemic complications, complex cardiac disease: not ideal candidates for transplantation[a]
RA pressures	Increased with decompensation	May rise due to causes independent of PAH (eg, intracardiac communication, valve disease)

[a]In some cases, combined heart-lung transplantation is necessary.
Reproduced with permission from *Curr Opin Cardiol.*[20]
Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; ES, Eisenmenger's syndrome; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PFO, patent foramen ovale; RA, right atrium; R-L, right-to-left; VSD, ventricular septal defect.

few differences were noted in hemodynamic parameters and no differences in 2-year survival from enrollment.[30] These analyses were complicated by the lack of classification according to ES status in patients with CHD-APAH with unrepaired lesions.

Diagnosis of Patients with PAH and CHD: The TACH Program Experience at Texas Children's Hospital

The large variability in PAH prevalence in patients with CHD may be due, in part, to the difficulties in diagnosing PAH in this population. In the patient with CHD, initial symptoms of PAH may also be attributed to CHD and/or cardiovascular disease progression. The European Society of Cardiology, American College of Chest Physicians, ACC, American Heart Association (AHA), American Thoracic Society, and the Pulmonary Hypertension Association have published expert consensus guidelines on the diagnosis and treatment of PAH,[3,31,32] and the ACC and AHA have published guidelines for assessment of PAH in patients with ACHD.[8] Early symptoms of PAH development are described in Table 3. Common symptoms of PAH that may also be attributed to CHD include dyspnea, decreased exercise tolerance, cyanosis, dizziness, and pallor.

As patients with CHD age, they commonly continue their care with their pediatric cardiologist because of the cardiologist's familiarity with their clinical history. Although pediatric cardiologists may be familiar with the cardiac complications that develop in ACHD patients (eg, arrhythmias, ventricular dysfunction, and the need for reoperation), they may not be prepared for acquired cardiovascular disease and other medical problems and conditions that are common in adults, including hypertension, hyperlipidemia, atherosclerosis, pregnancy, tobacco abuse, and noncompliance.[12,17,33] Conversely, the adult cardiologist may not be familiar with patients with CHD because they typically care for acquired heart disease.

The Web sites for the International Society for Adult Congenital Heart Disease (www.isachd.org) and the Adult Congenital Heart Association (www.achaheart.org) show that 87 clinics specialize in ACHD throughout the United States and Canada. These centers work to address the specific needs of the patient with ACHD, as identified in

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Table 3. Common Symptoms of PAH[20,31,32,46]

Diagnostic criteria for PAH requires right heart catheterization and includes:
Mean pulmonary artery pressure ≥ 25 mm Hg
Mean pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure ≤ 15 mm Hg
Symptoms that may be present include:
Dyspnea
Syncope
Fatigue
Weakness
Angina
Physical signs that may be present include:
Left parasternal lift
Accentuated pulmonary component of S2
Pansystolic murmur of tricuspid regurgitation
Diastolic murmur of pulmonary insufficiency
Right ventricular systolic dysfunction
Jugular vein distention
Hepatomegaly
Peripheral edema
Ascites
Cyanosis
Cool extremities
Abdominal distension
Abnormal laboratory findings that may be present include:
Electrocardiograph
Chest radiograph
Echocardiograph

Abbreviation: PAH, pulmonary arterial hypertension.

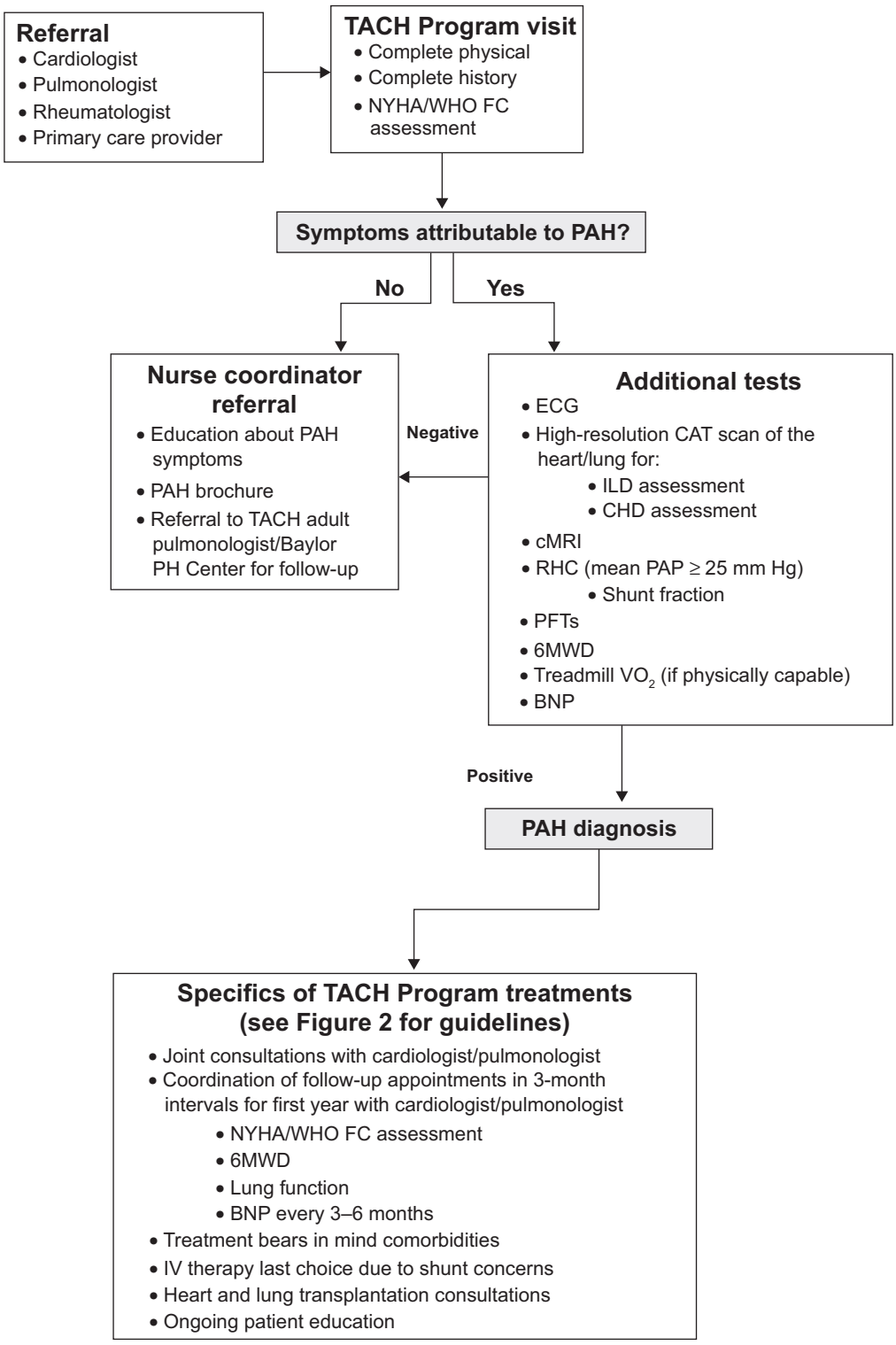
the ACC/AHA guidelines for ACHD.[8] The TACH Program began as a collaborative effort across Baylor College of Medicine's sections of adult cardiology and pediatric cardiology, Texas Children's Hospital, and the Texas Heart Institute at St. Luke's Episcopal Hospital in Houston. Our ACHD Center currently conducts > 1200 patient visits per year for > 4000 patients with ACHD.

The TACH Program transitions adolescents to adult care at age 16 years, at which time they are introduced to the ACHD cardiologist and the ACHD team. Our model consists of the following personnel, as suggested by the guidelines[8]: pediatric and adult cardiologists who work at both pediatric and adult facilities and are board certified in adult cardiology and/or pediatric cardiology; pediatric and adult pulmonologists; and internal medicine/pediatrics-trained primary care providers. There is also a group of 4 dedicated ACHD cardiac surgeons and 6 cardiac anesthesiologists. Other members include 2 nurse clinicians, a medical assistant, and 2 social workers. The ACHD team works with the patient and their parent(s) or guardian(s) to transition health care responsibilities from the parent to the patient, and they educate the young adult about the unique medical interests of the patient with ACHD. It is estimated that 55% of the ACHD population is at significant risk for premature death, reoperation, or complications including the development of PAH.[33]

Of the 1200 patients with ACHD seen at the TACH Program annually, approximately 7% are diagnosed with PAH, and nearly 40% of these patients with PAH have ES. A flow chart of initial assessment of a patient with ACHD at the TACH Program with symptoms that may be attributed to PAH is shown in Figure 1. Of note, the initial assessment involves the patient's self-assessment of his or her quality of life and physical state, according to the Minnesota Living With Heart Failure questionnaire. Referrals to the TACH Program are usually initiated by referring physicians, including primary care providers as well as pediatric or adult subspecialists, which often include pediatric or adult cardiologists. Signs and symptoms identified by the referring physician include shortness of breath, dyspnea on exertion, fatigue, cyanosis, worsening exercise tolerance, or syncope. Often, the first suggestion of PAH is noted on a transthoracic echocardiogram, which is frequently ordered in the evaluation of dyspnea. Since echocardiography is often used in the evaluation for dyspnea, it is commonly employed as a screening test, and patients may be referred to our program based on the abnormal echocardiogram alone. If the patient with ACHD has signs or symptoms suggestive of PAH (eg, cyanosis, dyspnea on exertion, or clubbing), additional tests are performed to confirm the diagnosis of PAH, which include echocardiography and may include RHC if the echocardiogram is highly suggestive of PAH. Echocardiography is used to estimate and RHC is used to measure cardiopulmonary hemodynamics in patients with PAH. A recent report demonstrated that echocardiography-estimated right ventricular systolic pressure and mean right atrial pressure correlated with the values measured using RHC[34]; however, the changes in these values over time showed no correlation. Thus, echocardiography may be sufficient for evaluation at a discrete time point; however, it lacks the functionality of RHC necessary to determine serial changes in cardiopulmonary hemodynamics.

If the patient is not diagnosed with PAH, he or she is educated about the potential to develop PAH by a nurse clinician, who also distributes a brochure with information about his or her heart disease and patient resources (including Web sites). Patients who are not diagnosed with PAH will continue routine cardiology follow-up, including annual echocardiograms to assess PAP. The nurse then coordinates a referral to our adult pulmonologists and PAH clinic if the patient desires additional information about his or her

Figure 1. Treatment algorithm for adult patients with CHD with PAH, derived from the experiences of the TACH Program. Patients are referred from community physicians, and their initial TACH Program visit determines whether their symptoms are attributable to PAH. If symptoms are not representative of PAH, the patient is educated about PAH and a follow-up is scheduled; if symptoms are attributable to PAH, a detailed assessment is performed. Once diagnosed with PAH, patients undergo treatment in accordance with guidelines and standard operating procedures.



Abbreviations: 6MWD, 6-minute walk test distance; BNP, B-type natriuretic peptide; CAT, computerized axial tomography; CHD, congenital heart disease; cMRI, cardiovascular magnetic resonance imaging; ECG, electrocardiogram; FC, functional class; ILD, interstitial lung disease; IV, intravenous; NYHA/WHO FC, New York Heart Association/World Health Organization functional class; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PFTs, pulmonary function tests; PH, pulmonary hypertension; RHC, right heart catheterization; TACH, Texas Adult Congenital Heart.

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Table 4. Studies That Investigate PAH Therapies in Patients with CHD or ES

Study	Intervention	Duration	N	Conclusions
Endothelin receptor antagonist: bosentan				
Christensen et al[49]	Bosentan 125 mg bid	5–14 months	ES: 9	67% improved NYHA FC $\geq$ 1; 9% increase in O_2 saturation; minimal side effects
Apostolopoulou et al[44]	Bosentan $>$ 40 kg, 125 mg bid 20–40 kg, 62.5 mg bid 10–20 kg, 31.25 mg bid	16 weeks	CHD-APAH: 7 ES: 15 (includes pediatric patients)	59% improved NYHA FC $\geq$ 1 1.5-mL/kg/min improvement in O_2 saturation 42-m increase in 6MWD 0.6 decrease in Borg dyspnea index Significant improvements in hemodynamics Minimal side effects 2 deaths in patients at NYHA FC IV at baseline and III at death
Schulze-Neick et al[50]	Bosentan 125 mg bid	2.1 $\pm$ 0.5 years	CHD-APAH: 10 ES: 23	Mean NYHA FC improved from 3.1 to 2.4 72-m increase in 6MWD 5-mm Hg decrease in right ventricular systolic pressure Minimal side effects
Benza et al[51]	Bosentan 125 mg bid	12 months	CHD-APAH: 24 (ES unspecified)	NYHA FC improvement Significant improvements in hemodynamics Minimal side effects 3 discontinuations due to elevated liver enzymes
Kourouklis et al[52]	Bosentan 125 mg bid	6 months	ES: 1	NYHA FC improvement from IV to III 10% increase in arterial O_2 saturation
Galie et al (BREATHE-5)[42]	Bosentan 125 mg bid (n = 37) Placebo (n = 17)	16 weeks	ES: 54	13/37 receiving bosentan improved WHO FC from III to II 53.1-m increase in 6MWD; significant improvements in hemodynamics; minimal side effects; 1 patient discontinued due to elevated liver enzymes
Sitbon et al[53]	Bosentan 125 mg bid	18.3 $\pm$ 9.9 months	CHD-APAH: 27 (ES unspecified)	13/27 improved NYHA FC $\geq$ 1 66-m increase in 6MWD
Ibrahim et al[54]	Bosentan 125 mg bid	16 weeks	CHD-APAH: 9 ES: 2	50% improved WHO FC from III to II 28-m increase in 6MWD Borg dyspnea index improvement Minimal side effects
D'Alto et al[55]	Bosentan 125 mg bid	1 year	CHD-APAH: 22 (ES unspecified)	Mean WHO FC improved from 3.1 to 2.5 6% improvement in O_2 saturation 74-m increase in 6MWD Significant improvements in hemodynamics Minimal side effects; 3 patients had elevated liver enzymes alleviated by dose reduction
Apostolopoulou et al[56]	Bosentan 125 mg bid	2.4 $\pm$ 0.1 years	CHD-APAH: 6 ES: 13	NYHA improvements achieved in the first 16 weeks (30) of treatment were maintained over 2 years Exercise parameters returned to baseline (pre-bosentan) levels
van Loon et al[57]	Bosentan $>$ 40 kg, 125 mg bid 20–40 kg, 62.5 mg bid 10–20 kg, 31.25 mg bid	Median, 2.7 years	CHD-APAH: 4 ES: 26 (includes pediatric patients)	Mean WHO FC improvement from 4 months to 1.5 years; adults maintained improvement Increase in 6MWD from 4 months to 1.5 years; reversed at 2.7 years in children but not adults Beneficial effect of bosentan persisted longer in adults than children
Diller et al[58]	Bosentan 125 mg bid	Median, 29 months	CHD-APAH: 3 ES: 15	Improvements in WHO FC Increase in 6MWD Minimal side effects; 1 patient died from progressive heart failure
Mehta et al[59]	Bosentan 125 mg bid (n = 21) Sitaxsentan 100 mg (n = 3)	19 $\pm$ 12 months	ES: 24	92% improved WHO FC $\geq$ 1 78-m increase in 6MWD; 7% improvement in O_2 saturation Significant improvements in hemodynamics

(*Continued*)

Table 4. (*Continued*)

Study	Intervention	Duration	N	Conclusions
Duffels et al[60]	Bosentan 125 mg bid	Median, 22 months	CHD-APAH: 9 ES: 49	Increase in 6MWD for 6 months, returned to baseline by 12 months Minimal side effects; 1 patient with elevated liver enzymes alleviated by dose reduction
Endothelin receptor antagonist: ambrisentan				
Rowan et al[25]	Ambrisentan (dosage not reported)	188 ± 109 days	ES: 15	WHO FC improved in 20%, stable in 80% 31-m increase in 6MWD ($P < 0.009$ vs baseline) Arterial O_2 saturation remained stable Favorable hemodynamics in 5/5 patients tested 1 death, presumed pulmonary embolus
Phosphodiesterase type-5 (PDE-5) inhibitor: sildenafil				
Lim et al[61]	Sildenafil 12.5–50 mg tid	Up to 16 months	CHD-APAH: 3	2 patients had 88–110 m (36%–60%) increase in 6MWD by 12–15 months Improvement in arterial saturation (maximal at 3 months) No significant side effects
Chau et al[62]	Sildenafil 25 mg tid then 25–50 mg tid PO	6 months	IPAH: 6 ES: 7	Significant improvement in mean NYHA FC by 6 months in both ES (3.3–2.1) and IPAH (3.0–2.2) Significant improvement in O_2 saturation by 6 months in ES (10%) but not in IPAH; improvement in 6MWD by 6 months: 28 m in ES, 35 m in IPAH Significant improvement in pulmonary hemodynamics in ES but not in IPAH
Garg et al[63]	Sildenafil 12.5 mg tid ≤ 25 kg, 25 mg tid 25–50 kg, 50 mg tid > 50 kg, 200 mg tid PO	18.7 ± 8.8 months	IPAH: 23 ES: 21 (includes pediatric patients)	Significant improvement in NYHA FC in all patients (by ≥ 1 FC) at mean follow-up of 18.7 months Significant improvement in 6MWD (118.9-m increase) Significant decrease in mean PAP (10.1 mm Hg) Benefits seen as early as 2 weeks and maximal with sildenafil 150 mg/day Generally well tolerated; 2 cases of rhinorrhea, 1 each of body ache and headache
Prostacyclin analogue: iloprost				
Rimensberger et al[64]	Inhaled iloprost 25 ng/kg/min for 10 minutes	10 minutes	CHD-APAH: 15	Iloprost as effective as NO in lowering PVR; iloprost + NO was no more effective than each alone
Durongpisitkul et al[65]	Inhaled iloprost 20–80 μg/day and oral beraprost 1–4 μg/kg/day	1 year	CHD-APAH: 23	At 12 months, 6MWD improved by 40 m WHO FC improved No difference in O_2 saturation
Okyay et al[66]	Inhaled iloprost 10 μg/10 min inhaled and sildenafil 50 mg PO	2 years	ES: 1	NYHA FC improvement from IV to II by 6 weeks and maintained over 2 years Improved 6MWD by 28 m; 5% improvement in O_2 saturation Improvements in hemodynamics
Reichenberg et al[67]	Inhaled iloprost ≤ 140 μg/day	Up to 3 months	PAH: 63 (11 were CHD-APAH)	Short-term decrease in PEF and increase in percutaneous O_2 saturation No long-term (3 months) changes in pulmonary function tests Long-term increase in 6MWD by 48 m
Ivy et al[68]	Inhaled iloprost 0.625–7.5 μg/dose 5–9 times daily	6 months	IPAH: 12 CHD-APAH: 10	Acute lowering of PAP, FEV_1, and FEF; at 6 months, WHO FC improved in 35%, decreased in 15%, and was unchanged in 50%; 36% discontinued iloprost
Limsuwan et al[69]	Inhaled iloprost 0.5 μg/kg	1 dose	CHD-APAH: 18	13/18 considered responders Mean PVR decrease from 9.3 to 4.6 Wood units in responders; 8 responders underwent surgical correction; all survived

Abbreviations: 6MWD, 6-minute walk test distance; bid, 2 times per day; CHD, congenital heart disease; CHD-APAH, CHD-associated PAH; ES, Eisenmenger's syndrome; FC, functional class; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; IPAH, idiopathic PAH; NO, nitric oxide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PEF, preserved ejection fraction; PO, by mouth; PVR, pulmonary vascular resistance; tid, 3 times a day; WHO, World Health Organization.

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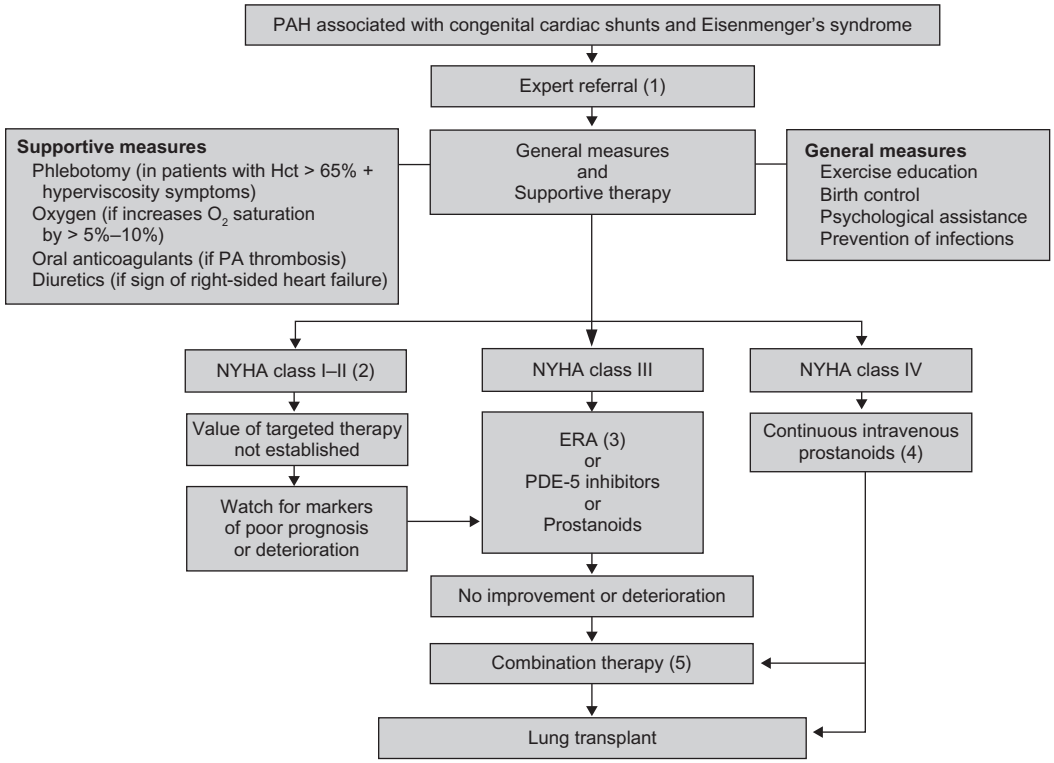
Figure 2. Treatment algorithm for patients with PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome (ES). **(1)** Owing to the complexity of the clinical condition and the treatment options available, it is strongly recommended that patients are referred to a specialized center. **(2)** Patients may remain mildly symptomatic (NYHA/WHO FC I and II) and clinically stable for prolonged periods of time, and the efficacy-to-safety ratio of the use of targeted therapies in this patient population has not been established. **(3)** There is greater evidence for the efficacy of the dual ERA bosentan because a specific randomized controlled trial has been performed with this compound.[42] **(4)** Most experts consider that patients with unstable NYHA class IV PAH should be treated with intravenous prostanoids, even if the presence of a central intravenous catheter may increase the risk of paradoxical embolization. **(5)** In patients with no improvement or deterioration, combination therapy should be considered in expert centers, even if no studies are available in this specific patient population.



Abbreviations: ERA, endothelin receptor antagonist; Hct, hematocrit; NYHA/WHO FC, New York Heart Association/World Health Organization functional class; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type-5.
Reproduced with permission from *Drugs*.[12]

condition. If the patient with ACHD is diagnosed with PAH, he or she is treated in consultation with the Baylor College of Medicine Pulmonary Hypertension Center (Baylor PH Center), particularly if more complex therapeutic regimens, including subcutaneous or inhalation therapy, are required.

Therapies Available for Patients with PAH and CHD

There are a number of recognized treatment options available for the management of CHD-APAH. Treatments that are supported by randomized clinical trials and approved by the US Food and Drug Administration (FDA) include the use of prostacyclin analogues, PDE-5 inhibitors, and ERAs.[35] Prostanoids (prostacyclins) were among the first class of drugs approved by the FDA for this indication. Exogenous prostanoids enhance endogenous production of prostacyclins, which is reduced in PAH,[36] and their application has been a successful therapeutic approach in the management of PAH.[37,38] The inhibition of PDE-5 slows the degradation of cyclic guanosine monophosphate and enhances dilatation of vascular smooth muscle. Endothelin receptor antagonists block the action of endothelin-1, a potent vasoconstrictor, which is elevated in patients with PAH.[39,40]

Clinical trials investigating PAH therapies routinely include patients with CHD-APAH as a subtype of patients with group 1 pulmonary hypertension.[12,41] Appreciation of the unique symptomatology of the patient with CHD-APAH or ES has resulted in several PAH studies targeting this specific population, although these studies have had small sample sizes and short treatment periods (Table 4). The majority of published studies in patients with ACHD-APAH investigate the use of an ERA or a PDE-5 inhibitor. In the first and only prospective, randomized, placebo-controlled clinical trial in patients with ES, the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5), there was a benefit in 6-minute walk test distance (6MWD) and World Health Organization (WHO) FC after 4 months of bosentan therapy.[42] However, additional trials with larger sample

sizes are needed to extend these findings beyond 4 months and to determine the risks and benefits of treatment with ERAs or PDE-5 inhibitors in patients with ACHD-APAH. Moreover, clinical trials investigating other types of CHD might support an expanded application of these potentially useful formulations.

A review of ERA therapy in patients with CHD with shunt-APAH (107 of 174 patients had ES) indicated that long-term treatment with bosentan improved NYHA/WHO FC by at least 1 in the majority of patients, improved 6MWD, and caused few side effects other than previously identified adverse events (eg, elevated hepatic transaminases).[43] In one study from 2005, however, 2 patients with WHO FC IV died during therapy.[44] The cause of 1 death was stated as "presumably due to arrhythmia"; the other death had a post-mortem examination that showed "generalized myocardial ischemia as a recent terminal event with possible arrhythmic death." It is important to note that arrhythmias are not a common side effect of ERAs, nor have these serious adverse events been suggested in the literature. Nonetheless, the benefit of bosentan therapy in patients with CHD with WHO FC IV PAH requires further investigation.

The survival benefits of advanced PAH therapy in patients with ES have recently been shown.[45] A retrospective analysis of 4-year data from 229 patients with ES who attended a single center showed that the 68 patients who had received advanced therapy (73.5% bosentan, 25% sildenafil, and 1.5% epoprostenol) had a significantly lower risk of death (adjusted hazard ratio, 0.16; $P = 0.015$) compared to patients who did not receive advanced treatment. Given these data, clinicians should strongly consider treating patients with ES with advanced therapy.

A treatment algorithm for patients with ACHD-APAH, based on studies in patients with CHD and PAH, is discussed in Figure 2. Adapted from treatment algorithms derived for patients with IPAH or APAH, this algorithm incorporates treatments that have been shown to be efficacious in all PAH subtypes, along with specific recommendations for the patient with CHD-APAH.[12] Of particular importance, the recommended first step of the CHD-APAH treatment algorithm includes a multidisciplinary approach (when available) at specialized ACHD care centers that are dedicated to the support of patients with ACHD.

The ACC has endorsed an updated evidence-based treatment algorithm in PAH recommending that all patients undergo acute vasoreactivity testing following expert referral to a specialized center.[46] Patients who display acute vasoreactivity should be treated with calcium channel blockers. For patients who are nonresponders to acute vasoreactivity testing, the guidelines recommend treatment with a PDE-5 inhibitor or an ERA for patients classified as WHO FC III. Nonresponders classified as WHO FC IV should be administered continuous intravenous prostanoids.[46] Although not explicitly recommended in the guidelines, we recommend starting treatment with advanced therapies targeted for patients in FC II due to the progressive nature of the disease. The benefits of treatment in patients with FC II PAH, including those with CHD-APAH, have been reported in the Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients (EARLY), a prospective, randomized, double-blind, multicenter, parallel-group study performed in 52 sites in 21 countries.[47] Thus, the application of PAH therapy may be warranted in patients with CHD-APAH in FC II.

The treatment algorithm for CHD-APAH and ES is comparable with the general PAH treatment algorithm; phlebotomies are recommended if hyperviscosity symptoms are present and hematocrit is $> 65\%$. Oral anticoagulants are indicated in patients with pulmonary artery thrombosis and/or absent to mild hemoptysis.[12] Targeted therapies, such as PDE-5 inhibitors or ERAs, are initiated in patients classified as NYHA FC III; intravenous therapies are recommended for patients with FC IV CHD-APAH.[12]

Treatment of Patients with PAH and CHD: The TACH Program Method

When the patient with ACHD is diagnosed with PAH after RHC, we institute a treatment algorithm specific for CHD-APAH, derived from the ACHD guidelines and reviewed in Figure 2.[8] For initial therapy, oral agents that address the endothelial dysfunction associated with PAH are generally instituted in FC I–III. (Intravenous agents are often unsafe due to the presence of residual cardiac shunts that can predispose the patient to paradoxical embolism.) Oral agents include the ERAs bosentan or ambrisentan, or the PDE-5 inhibitors sildenafil or tadalafil. Although there are insufficient data to determine which oral agent is best for treatment initiation, the BREATHE-5 study (the only randomized placebo-controlled clinical trial in patients with ES) showed clinical improvement with bosentan therapy.[42]

We monitor the response to therapy in patients using both clinical parameters (eg, echocardiography and 6MWD) and patient self-reporting (eg, exercise tolerance and symptoms) during clinic visits 3 and 6 months after starting therapy. If the patients demonstrate clinical improvement, the regimen will be maintained. If signs of deterioration are

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noted, then another oral agent from a different class may be added (eg, add sildenafil to bosentan). These patients are then followed closely over the next 3 months to assess their response to therapy.

If the patient does not improve after sufficient time (often at least 3 months) on 2 oral agents, then we typically progress to prostacyclin therapy, often with subcutaneous treprostinil. Inhaled iloprost is another option to be considered. Although intravenous prostacyclin (epoprostenol) is often considered for nonresponders to oral therapy, indwelling catheters and intravenous infusions should generally be avoided in patients with right-to-left intracardiac shunts because of the high risk of paradoxical embolism and stroke.

Patients with complex ACHD, such as those who continue to deteriorate on combination therapy, those on subcutaneous prostacyclin, or those who are NYHA FC IIIB/IV, are managed in conjunction with the Baylor PH Center. For these patients, referral for lung transplant should be considered, or heart-lung transplantation for patients with ES and intracardiac and/or systemic-to-pulmonary shunts that cannot be repaired at the time of lung transplant. At our center, only 0.4% of our patients are referred annually for heart-lung transplant.

Patient Support Programs at the TACH Program

We have instituted several support mechanisms for patients with PAH, recognizing that patient education is valuable for ongoing compliance. All patients are given brochures on PAH, which provide a general introduction. Patients are also encouraged to learn specifically about PAH from the Pulmonary Hypertension Association (www.phassociation.org) and more about ACHD through the Adult Congenital Heart Association (www.achaheart.org) and the International Society for Adult Congenital Heart Disease (www.isachd.org). Information about online and local support groups is available through these Web sites. Due to the high monthly costs of these medicines (range: $1200–3500/month if not covered by health insurance), discounts can be provided by the pharmaceutical companies via their patient assistance programs. In addition, financial assistance is sometimes offered by local and national charities (eg, the Caring Voice Coalition). Patients are also referred to our institution's social workers and financial counselors who are familiar with these cases. Finally, the TACH Program and Baylor College of Medicine also participate in ongoing clinical trials in PAH, and eligible patients are notified and provided the opportunity to participate.

Summary

As pediatric cardiovascular interventions have improved in recent decades, a growing proportion of pediatric patients with CHD are reaching adulthood. It has become increasingly apparent that patients with ACHD have distinct medical needs that are best met through specialized regional ACHD centers of excellence.[8] An awareness of the signs and symptoms of PAH in ACHD is particularly important due to the prognosis of this disease, and specialized ACHD centers can facilitate the coordination of cardiologists, pulmonologists, and support personnel to educate, support, and treat patients with ACHD who develop PAH. Collaborative care with a PAH clinic may be instrumental in achieving this goal.

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Conflict of Interest Statement

Wayne J. Franklin, MD, FACC is on the speaker's bureau for Actelion and receives research grant support from Medtronic and St. Jude Medical. Dhaval R. Parekh, MD has no conflicts of interest to disclose. Zeenat Safdar, MD, FCCP, FACP is a consultant and is on advisory boards and speakers' bureaus for Actelion, Gilead, and United Therapeutics, and is on the advisory board for Bayer.

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