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Chest 2007;131;1917-1928
DOI 10.1378/chest.06-2674

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CHEST Clinical Practice Guidelines

Medical Therapy for Pulmonary Arterial Hypertension*

Updated ACCP Evidence-Based Clinical Practice Guidelines

David B. Badesch, MD, FCCP; Steven H. Abman, MD; Gerald Simonneau, MD; Lewis J. Rubin, MD, FCCP; and Vallerie V. McLaughlin, MD, FCCP

A consensus panel convened by the American College of Chest Physicians developed guidelines for the treatment of pulmonary arterial hypertension (PAH) that were published in 2004. Subsequently, several important clinical trials have been published, and new treatments have received regulatory approval. In addition, add-on and combination therapy are being explored, which promise to open new therapeutic avenues. This article, taking into consideration studies published prior to September 1, 2006, provides an update to the previously published guidelines. The original guidelines have been summarized, a discussion of new studies has been added, and the treatment algorithm has been revised to take into account recent developments in therapy. This update provides evidence-based treatment recommendations for physicians involved in the care of patients with PAH. Due to the complexity of the diagnostic evaluation required and the treatment options available, referral of patients with PAH to a specialized center continues to be strongly recommended. ***(CHEST 2007; 131:1917–1928)***

Key words: anticoagulation; arginine; beraprost; bosentan; calcium-channel blockers; endothelin; endothelin receptor antagonist; epoprostenol; idiopathic pulmonary arterial hypertension; iloprost; medical therapy; oxygen; primary pulmonary hypertension; prostacyclin; pulmonary arterial hypertension; pulmonary hypertension; secondary pulmonary hypertension; sildenafil; therapy; treatment; treprostinil; vasoreactivity; warfarin

Abbreviations: ACCP = American College of Chest Physicians; CCB = calcium-channel blockers; FDA = Food and Drug Administration; IPAH = idiopathic pulmonary arterial hypertension; 6MW = 6-min walk; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized clinical trial

Pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure (PAPm) ≥ 25 mm Hg with a pulmonary capillary wedge pressure ≤ 15 mm Hg measured by cardiac catheterization, is a disorder that may occur either in the setting of a variety of underlying medical conditions or as a disease that uniquely affects the pulmonary circulation. Irrespective of its etiology, PAH is a serious and often progressive disorder that results in right ventricular dysfunction and impairment in activity tolerance, and may lead to right-heart failure and death. The pathogenesis of PAH is complex and incompletely understood, but includes both genetic and environmental factors that alter vascular structure and function.

Dramatic advances in the treatment of PAH have occurred over the past 2 decades, based in part on seminal observations on pathogenesis made in the research laboratory. Recognizing the need to educate physicians on the diagnosis and management of PAH, the American College of Chest Physicians (ACCP) convened a multidisciplinary panel of experts from 2003 to 2004 to formulate guidelines for the approach to management of this complex condition. These evidence-based guidelines, including a comprehensive overview of treatment,[1] were published as a supplement to *CHEST* in 2004.[1–8] The guidelines from this original publication are presented in Table 1.

The pace of developments in the treatment for PAH has quickened, with several important clinical trials having been published over the past 2 years that have led to regulatory approval of newer drugs and experience with combinations of existing drugs. These advances are likely to impact on the way physicians should now approach the treatment of

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PAH. Accordingly, the ACCP impaneled a subcommittee of the original panel to develop an update to the treatment guidelines based on these recent developments. As before, these guidelines are evidence based and the subcommittee employed the same criteria for inclusion and recommendation as were used in the previous work.

Update of Treatment Guidelines

A consensus panel convened by the ACCP developed guidelines for the diagnosis and treatment of PAH that were published in 2004.[9] Subsequently, several important clinical trials have been published and new treatments have received regulatory approval. In addition, add-on and combination therapy are being explored, which promise to open new therapeutic avenues.

Therefore, the Health and Science Policy Committee of the ACCP authorized an update of the medical treatment guidelines.[1] Lewis Rubin, MD, FCCP, was again selected to chair the panel. A small subset of authors from the original guideline were requested to participate in the update. In October 2005, the group met in Montreal to plan the revision and to cultivate consensus on the approach to the new treatment algorithm.

The authors performed computerized searches of the literature for studies on the medical treatment of PAH that were published prior to September 1, 2006. Only English-language articles were included. We selected studies of therapeutic agents in the following classes: prostanoids, endothelin receptor antagonists, and phophodiesterase inhibitors. As in the previous guidelines,[1] we considered studies conducted among patients with known or suspected idiopathic PAH (IPAH) or PAH occurring in association with underlying collagen vascular disease, and congenital heart disease. Also in a manner consistent with the previous statement, we excluded studies of pulmonary hypertension (PH) associated with COPD or other parenchymal lung disease, high-altitude PH, or cardiac disease (*eg*, left-heart failure, valvular heart disease) except congenital heart disease. This article provides an update to the previously published guidelines based on this current body of literature. The original guidelines have been summarized, a discussion of new studies has been added, and the treatment algorithm has been revised to take into account recent developments in therapy. The recommendations in this guideline, like those in the 2004 edition, are based on the same grading system (Table 2), in which the strength of the recommendation results from the interaction of two components: the quality of the evidence, and the net benefit of the therapy to the patient[4] (Table 3).

This update provides evidence-based treatment recommendations for physicians involved in the care of patients with PAH. No financial support was provided by any pharmaceutical companies for the development of this update. Any conflicts of interest were required to be disclosed by all authors and included in this document. This guideline was reviewed and approved by the Pulmonary Vascular NetWork, Health and Science Policy Committee, and ultimately by the Board of Regents of the ACCP.

Calcium-Channel Antagonists

A small number of patients with IPAH, who demonstrate a favorable response to acute vasodilator testing at the time of cardiac catheterization, will do well with calcium-channel blocker (CCB)

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Dr. Simonneau has received grant monies from, served on the speaker's bureau for, and served on the advisory committees for Actelion, Pfizer, Schering, United Therapeutics, and GlaxoSmithKline.
Dr. Rubin has received university grant monies from the National Heart, Lung, and Blood Institute. He has received grant monies from Actelion, Pfizer, United Therapeutics, Mondo-Biotech, MD Primer, and Gilead. He is a shareholder in LungRx. He has received consultant fees from the National Heart, Lung, and Blood Institute; Actelion; Pfizer; United Therapeutics; ProQuest; Bayer Schering; and Mondo-Biotech. He is on the advisory committees for Actelion, Pfizer, LungRx, MD Primer, and Encysive.
Dr. McLaughlin has received grant monies from Actelion, Encysive, LungRx, Pfizer, and United Technologies. She has served on the speaker's bureau and advisory committees for Actelion, Gilead, and Pfizer.
Manuscript received November 1, 2006; revision accepted February 9, 2007.

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DOI: 10.1378/chest.06-2674

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Table 1—*Summary of Recommendations From the First Edition of this Guideline

Guideline No.	Recommendations	Grading†
Screening, early detection, and diagnosis of PAH		
1	Genetic testing and professional genetic counseling should be offered to relatives of patients with familial PAH.	Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/A
2	Patients with IPAH should be advised about the availability of genetic testing and counseling for their relatives.	Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/A
3	In patients with a suspicion of PAH, ECG should be performed to screen for a spectrum of cardiac anatomic and arrhythmic problems. ECG lacks sufficient sensitivity to serve as an effective screening tool for PAH but contributes prognostic information in patients with known PAH.	Quality of evidence: low; benefit: small/weak; strength of recommendation: C
4	In patients with a suspicion of PAH, chest radiography should be performed to reveal features supportive of a diagnosis of PAH and to lead to diagnoses of underlying diseases.	Quality of evidence: low; benefit: intermediate; strength of recommendation: C
5	In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as a noninvasive screening test that can detect PH, although it may be imprecise in determining actual pressures compared to invasive evaluation in a portion of patients.	Quality of evidence: fair; benefit: substantial; strength of recommendation: A
6	In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed to evaluate the level of right ventricular systolic pressure and to assess the presence of associated anatomic abnormalities such as right atrial enlargement, right ventricular enlargement, and pericardial effusion.	Quality of evidence: expert opinion, benefit: intermediate; strength of recommendation: E/B
7	In asymptomatic patients at high risk, Doppler echocardiography should be performed to detect elevated pulmonary arterial pressure.	Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/B
8	In patients with suspected or documented PH, Doppler echocardiography should be obtained to look for left ventricular systolic and diastolic dysfunction, left-sided chamber enlargement, or valvular heart disease.	Quality of evidence: good; benefit: substantial; strength of recommendation: A
9	In patients with suspected or documented PH, Doppler echocardiography with contrast should be obtained to look for evidence of intracardiac shunting.	Quality of evidence: fair; benefit: intermediate; strength of recommendation: B
10	In patients with unexplained PAH, testing for connective tissue disease and HIV infection should be performed.	Quality of evidence: expert opinion; benefit: intermediate; strength of recommendation: E/A
11	In patients with PAH, ventilation-perfusion scanning should be performed to rule out CTEPH; a normal scan effectively excludes a diagnosis of CTEPH.	Quality of evidence: low; benefit: substantial; strength of recommendation: B
12	In patients with PAH, contrast-enhanced chest CT or MRI should not be used to exclude the diagnosis of CTEPH.	Quality of evidence: low; benefit: negative; strength of recommendation: D
13	In patients with PAH and a ventilation/perfusion scan suggestive of CTEPH, pulmonary angiography is required for accurate diagnosis and best anatomic definition to assess operability.	Quality of evidence: expert opinion; benefit: substantial; strength of recommendation: E/A
14	In patients with PAH, testing of pulmonary function and arterial blood oxygenation should be performed to evaluate for the presence of lung disease.	Quality of evidence: low; benefit: substantial; strength of recommendation: B
15	In patients with systemic sclerosis, pulmonary function testing with DLCO should be performed periodically (every 6 to 12 mo) to improve detection of pulmonary vascular or interstitial disease.	Quality of evidence: fair; benefit: intermediate; strength of recommendation: B
16	In patients with PAH, lung biopsy is not routinely recommended because of the risk, except under circumstances in which a specific question can only be answered by tissue examination.	Quality of evidence: expert opinion; benefit: substantial; strength of recommendation: E/A
17	In patients with suspected PH, right-heart catheterization is required to confirm the presence of PH, establish the specific diagnosis, and determine the severity of PH.	Quality of evidence: good; benefit: substantial; strength of recommendation: A
18	In patients with suspected PH, right-heart catheterization is required to guide therapy.	Quality of evidence: low; benefit: substantial; strength of recommendation: B
19	In patients with PAH, serial determinations of functional class and exercise capacity assessed by the 6MW test provide benchmarks for disease severity, response to therapy, and progression.	Quality of evidence: good; benefit: intermediate; strength of recommendation: A
Medical therapy for PAH		
1	Patients with IPAH should undergo acute vasoreactivity testing using a short-acting agent such as IV epoprostenol, adenosine, or inhaled nitric oxide.	Level of evidence: fair; benefit: substantial; grade of recommendation: A
2	Patients with PAH associated with underlying processes, such as scleroderma or congenital heart disease, should undergo acute vasoreactivity testing.	Level of evidence: expert opinion; benefit: small/weak; grade of recommendation: E/C
3	Patients with PAH should undergo vasoreactivity testing by a physician experienced in the management of pulmonary vascular disease.	Level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A
4	Patients with IPAH, in the absence of right-heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in PAPm of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or unchanged cardiac output), should be considered candidates for a trial therapy with an oral calcium-channel antagonist.	Level of evidence: low; benefit: substantial; grade of recommendation: B
5	Patients with PAH associated with underlying processes such as scleroderma or congenital heart disease, in the absence of right-heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in pulmonary artery pressure of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or unchanged cardiac output), should be considered candidates for a trial of therapy with an oral calcium-channel antagonist.	Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/B
6	In patients with PAH, CCBs should not be used empirically to treat PH in the absence of demonstrated acute vasoreactivity.	Level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A
7	Patients with IPAH should receive anticoagulation with warfarin.	Level of evidence: fair; benefit: intermediate; grade of recommendation: B
8	In patients with PAH occurring in association with other underlying processes, such as scleroderma or congenital heart disease, anticoagulation should be considered.	Level of evidence: expert opinion; benefit: small/weak; grade of recommendation: E/C
9	In patients with PAH, supplemental oxygen should be used as necessary to maintain oxygen saturations at > 90% at all times.	Level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A.
16	Children with PAH:	
a	With right-heart failure or with hypercoagulable state, administer anticoagulation with warfarin.	Level of evidence: expert opinion; net benefit: intermediate; strength of recommendation: E/B
b	Without right-heart failure or with hypercoagulable state, administer anticoagulation with warfarin; for children < 5 years of age, lower target international normalized ratios are recommended.	Level of evidence: expert opinion; net benefit: small/weak; strength of recommendation: E/C
17	In patients with PAH, pregnancy should be avoided, or termination recommended.	Level of evidence: good; benefit: substantial; grade of recommendation: A

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Table 1—*Continued*

Guideline No.	Recommendations	Grading†
Surgical treatments/interventions for PAH		
1	In select patients with PAH unresponsive to medical management, atrial septostomy should be considered.	Quality of evidence: low; net benefit: intermediate; strength of recommendation: C
2	In patients with PAH, atrial septostomy should be performed only at institutions with significant procedural and clinical experience.	Quality of evidence: expert opinion; net benefit: substantial; strength of recommendation: E/A
3	Patients with suspected CTEPH should be referred to centers experienced in the procedure for consideration of pulmonary thromboendarterectomy.	Level of evidence: expert opinion; benefit: substantial; grade of recommendation: E/A
4	In patients with operable CTEPH, pulmonary thromboendarterectomy is the treatment of choice for improved hemodynamics, functional status, and survival.	Level of evidence: low; benefit: substantial; grade of recommendation: B
5	In patients with CTEPH deemed inoperable or with significant residual postoperative PH, balloon dilation, PAH medical therapy, or lung transplantation may be considered.	Level of evidence: low; benefit: small/weak; grade of recommendation: C
6	PAH patients with NYHA functional class III and IV symptoms should be referred to a transplant center for evaluation and listing for lung or heart-lung transplantation	Level of evidence: low; benefit: substantial: grade of recommendation: B
7	Listed patients with PAH whose prognosis remains poor despite medical therapy should undergo lung or heart-lung transplantation	Level of evidence: fair; benefit: substantial: grade of recommendation: A
8	In patients with PAH who are undergoing transplantation, the procedure of choice is a bilateral lung transplant.	Level of evidence: low; benefit: Intermediate; grade of recommendation: C
9	In children with PAH who are undergoing transplantation, the procedure of choice is a bilateral lung transplant.	Level of evidence: low; benefit: substantial; grade of recommendation: B
10	In adult patients with PAH and simple congenital heart lesions, bilateral lung transplant with repair of the cardiac defect is the procedure of choice.	Level of evidence: low; benefit: intermediate; grade of recommendation: C
11	In adult patients with PAH and complex congenital heart disease who are undergoing transplant, HLT is the procedure of choice.	Level of evidence: low; benefit: Substantial; grade of recommendation: B
PAH and sleep-disordered breathing		
1	In the evaluation of patients with PAH, an assessment of sleep-disordered breathing is recommended.	Quality of evidence: low; net benefit: small/weak; strength of recommendation: C
2	In the evaluation of a patient with PAH for sleep-disordered breathing, polysomnography is recommended if OSA is suspected as the etiology, if a screening test for OSA is positive, or if a high clinical suspicion for OSA is present.	Quality of evidence: expert opinion; net benefit: intermediate; strength of recommendation: E/B
3	In the management of patients with OSA, routine evaluation for the presence of PAH is not recommended.	Quality of evidence: low; net benefit: none; strength of recommendation: I
4	In patients with OSA and PAH, treatment of OSA with positive airway pressure therapy should be provided with the expectation that pulmonary pressures will decrease, although they may not normalize, particularly when PAH is more severe.	Quality of evidence: low; net benefit: small/weak; strength of recommendation: C
Prognosis of PAH		
1	Advance NYHA functional class.	Quality of evidence: good; net benefit: substantial; strength of recommendation: A
2	Low 6MW distance.	Quality of evidence: good; net benefit: substantial; strength of recommendation: A
3	Presence of a pericardial effusion.	Quality of evidence: good; net benefit: substantial; strength of recommendation: A
4	Elevated mean right atrial pressure.	Quality of evidence: fair; net benefit: substantial; strength of recommendation: A
5	Reduced cardiac index.	Quality of evidence: fair; net benefit: substantial; strength of recommendation: A
6	Elevated PAPm.	Quality of evidence: fair; net benefit: intermediate; strength of recommendation: B
7	Elevated Doppler right ventricular ([tei]) index.	Quality of evidence: low; net benefit: intermediate; strength of recommendation: C
8	Low $\dot{V}o_2$max and low peak exercise systolic and diastolic BP as determined by cardiopulmonary exercise testing.	Quality of evidence: low; net benefit: intermediate; strength of recommendation: C
9	ECG findings of increased P wave amplitude in lead II, qR pattern in lead V1, and World Health Organization criteria for right ventricular hypertrophy.	Quality of evidence: low; net benefit: intermediate; strength of recommendation: C
10	Elevated brain natriuretic peptide (> 180 pg/mL).	Quality of evidence: low; net benefit: intermediate; strength of recommendation: C
11	In patients with IPAH treated with epoprostenol, persistence of NYHA functional class III or IV status after at least 3 mo of therapy may be used to predict a worse prognosis.	Quality of evidence: fair; net benefit: substantial; strength of recommendation: A
12	In patients with scleroderma associated PAH, reduced DLCO (< 45% of predicted) may be used to predict a worse prognosis.	Quality of evidence: low; net benefit: small/weak; strength of recommendation: C
13	In pediatric IPAH patients, younger age at diagnosis may be used to predict a worse prognosis.	Quality of evidence: low; net benefit: small/weak; strength of recommendation: C

*CTEPH = chronic thromboembolic PH; DLCO = diffusion capacity of the lung for carbon monoxide; HLT = heart-lung transplant; OSA = obstructive sleep apnea; $\dot{V}o_2$max = maximum oxygen uptake.
†Recommendation designations are defined in Table 2.

therapy. Since publication of the original ACCP guidelines, an important article[10] has further clarified the role of CCBs in the IPAH population. Sitbon and colleagues[10] reported results of a retrospective analysis of 557 IPAH patients tested acutely with IV epoprostenol or inhaled nitric oxide. Using a criteria of a > 20% decrease in both PAPm and pulmonary vascular resistance (PVR), only 70 patients (12.6%) displayed vasoreactivity. Long-term CCB responders were defined as patients in New York Heart Association (NYHA) functional class I or II with a sustained hemodynamic improvement after at least 1 year without the addition of other PAH-specific therapy. Of the 70 patients who displayed acute vasoreactivity, only 38 patients (6.8% of the overall study group)

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Table 2—*Quality of Evidence, Net Benefit, and Strength of Recommendation*

Variables	Description
Quality of the evidence	
Good	Evidence is based on good randomized controlled trials or metaanalyses.
Fair	Evidence is based on other controlled trials or RCTs with minor flaws.
Low	Evidence is based on nonrandomized, case-control, or other observational studies.
Expert opinion	Evidence is based the consensus of the carefully selected panel of experts in the topic field. There are no studies that meet the criteria for inclusion in the literature review.
Net benefit	
Substantial	
Intermediate	
Small/weak	
None	
Conflicting	
Negative	
Strength of recommendation	
A	Strong recommendation
B	Moderate recommendation
C	Weak recommendation
D	Negative recommendation
I	No recommendation possible (inconclusive)
E/A	Strong recommendation based on expert opinion only
E/B	Moderate recommendation based on expert opinion only
E/C	Weak recommendation based on expert opinion only
E/D	Negative recommendation based on expert opinion only

had a favorable long-term clinical response to long-term CCB therapy. These patients exhibited a more pronounced reduction in PAPm, reaching an absolute PAPm of 33 ± 8 mm Hg (± SD) with acute vasodilator testing. As a result, the consensus definition of a favorable response is now defined as a fall in PAPm ≥ 10 mm Hg, to a PAPm ≤ 40 mm Hg, with an unchanged or increased cardiac output. Patients with IPAH who meet these criteria may be treated with CCBs. True responders to vasodilators (CCBs) are very uncommon among patients with other forms of PAH (non-IPAH, or PAH occurring in association with underlying disease processes). Long-acting nifedipine or diltiazem, or amlodipine are suggested. Due to its potential negative inotropic effects, verapamil should be avoided. Patients should be followed up closely for both safety and efficacy, with an initial reassessment after 3 months of therapy.[10] If a patient does not improve to functional class I or II, additional or alternative PAH therapy should be instituted.

PROSTANOIDS

Epoprostenol

In a 12-week, prospective, multicenter, randomized, controlled, open-label trial,[11] continuously IV infused epoprostenol plus conventional therapy (including oral vasodilators [CCBs], anticoagulation, diuretic, digoxin, and oxygen) was compared to conventional therapy alone in 81 patients with severe IPAH (NYHA class III or IV). Exercise capacity improved in the 41 patients treated with epoprostenol (median 6 min walk [6MW] distance, 362 m at 12 weeks, vs 315 m at baseline), and decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks vs 270 m at baseline; $p < 0.002$ for the comparison of the treatment groups). There were also improvements in indexes of the quality of life, hemodynamics, and

Table 3—*Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits**

	Net Benefit					
Quality of Evidence	Substantial	Intermediate	Small/Weak	None	Conflicting	Negative
Good	A	A	B	D	I	D
Fair	A	B	C	D	I	D
Low	B	C	C	I	I	D
Expert opinion	E/A	E/B	E/C	I	I	E/D

*See Table 2 for definition of designations.

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survival. A multicenter, randomized, controlled, open-label study[12] of long-term IV epoprostenol treatment in patients with PAH occurring in association with the scleroderma spectrum of disease showed improvement in exercise capacity and hemodynamics. Exercise capacity improved with epoprostenol (median 6MW distance, 316 m at 12 weeks, compared with 270 m at baseline) but decreased with conventional therapy (192 m at 12 weeks, compared with 240 m at baseline). The difference between treatment groups in the median distance walked at week 12 was 108 m (95% confidence interval CI, 55.2 m to 180.0 m) [$p < 0.001$]. Hemodynamics also improved, however a survival advantage was not demonstrated. Two large long term observation series have documented an improvement in survival in patients with IPAH treated with epoprostenol compared to either historical control subjects or predicted survival based on the National Institutes of Health Registry equation.[13,14]

Treprostinil

A placebo-controlled trial of subcutaneously infused treprostinil in patients with functional class II, III, or IV PAH (IPAH or PAH associated with connective tissue disease or congenital systemic to pulmonary shunts) demonstrated improved exercise capacity as measured by the 6-min walk (6MW) distance (median between treatment group difference 16 m ($p = 0.006$).[15] This effect appeared to be dose related, and subcutaneous dosing may be limited by infusion site pain and reaction. Given potential advantages over IV epoprostenol, including a longer half-life, IV treprostinil has been studied recently. In an open-label study, Tapson et al[16] treated 16 functional class III or IV PAH patients with IV treprostinil. After 12 weeks of therapy, 6MW distance improved by a mean of 82 m, from 319 ± 22 to 400 ± 26 m ($p = 0.001$) [± SE]. There were also improvements in hemodynamics including PAPm (− 4.2 mm Hg, $p = 0.03$), cardiac index (+ 0.47 L/min/m^2, $p = 0.002$), and PVR index (− 9.4 U/m^2, $p = 0.001$) at week 12 compared to baseline. One death, which was thought not to be related to the study drug, occurred during the 12-week study in a patient who received 3 days of IV treprostinil and died 2 weeks later. In a similar open-label trial, Gomberg-Maitland et al[17] transitioned 31 functional class II and III PAH patients from IV epoprostenol to IV treprostinil. Twenty-seven patients completed the 12-week study, and 4 patients were transitioned back to epoprostenol. Exercise endurance as measured by the 6MW distance was maintained among the patients completing the transition (438 ± 16 m at baseline, 439 ± 16 m at week 12) [± SD]. At week 12, there was a modest increase in PAPm of 4 ± 1 mm Hg ($p < 0.01$) and reduction in cardiac index of 0.4 ± 0.1 L/min/m^2 ($p = 0.01$). Notably, the dose of IV treprostinil at the end of 12 weeks was more than twice the dose of IV epoprostenol at the start of the study: 83 ng/kg/min vs 40 ng/kg/min. In 2004, the US Food and Drug Administration (FDA) approved the use of IV treprostinil in NYHA functional class II, III, and IV PAH patients in whom subcutaneous infusion is not tolerated.

Iloprost

A 3-month, randomized, double-blind, placebo-controlled, multicenter trial of iloprost via inhalation six to nine times per day utilized a composite primary end point of a 10% improvement in the 6MW distance and NYHA functional class improvement in the absence of clinical deterioration or death.[18] This composite end point was achieved in 17% of treated patients compared to 5% in patients receiving placebo ($p = 0.007$). The treatment effect on the 6MW distance was a mean increase of 36 m in the overall population in favor of iloprost ($p = 0.004$) and 59 m in the subgroup of patients with IPAH. Longer-term data regarding inhaled iloprost are conflicting. In a 1-year, open, uncontrolled study[19] of 24 patients with IPAH, aerosolized iloprost at a daily dose of 100 to 150 μg, six to eight inhalations per day improved exercise capacity (mean increase in 6MW distance, 75 m) and pulmonary hemodynamics. More recently, Opitz et al[20] prospectively followed up 76 NHYA functional class II or III IPAH patients treated with inhaled iloprost. During the follow-up period of 535 ± 61 days, 11 patients (14%) died, 6 patients (9%) underwent transplantation, 25 patients (33%) were switched to IV prostanoids, 16 patients (23%) received additional/oral PAH therapies, and 12 patients (17%) discontinued inhaled iloprost for other reasons. Event-free survival rates at 1 year and 2 years were 53% and 29%, respectively.

Most recently, inhaled iloprost has been studied in patients who remain symptomatic (NYHA functional class III or IV) while receiving a stable dose of bosentan for at least 3 months.[21] In this multicenter, placebo-controlled, randomized trial, 67 patients with PAH (94% NYHA functional class III; mean baseline 6MW, 355 m) were randomized to receive inhaled iloprost, (5 μg; six to nine times per day) or placebo. After 12 weeks, the primary efficacy measure, postinhalation 6-min walk distance, improved by 30 m in the iloprost group and 4 m in the placebo group, for a placebo-adjusted difference of + 26 m ($p = 0.051$). There were also improvements in NYHA functional class ($p = 0.002$), time to clinical worsening ($p = 0.022$), and postinhalation PAPm ($p < 0.001$) and PVR $p < 0.001$). Combination ther-

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apy appeared to be safe and well tolerated. Inhaled iloprost was approved by the FDA in 2004 for functional class III and IV PAH, and in 2005 a brief summary of the results of the add-on study was included in the package insert.

Endothelin Antagonists

Bosentan

The first randomized, double-blind, placebo-controlled, multicenter study[22] of bosentan demonstrated an improvement in the 6MW distance of 70 m (from 360 ± 19 m at baseline to 430 ± 14 m at week 12; $p < 0.05$), whereas no improvement was seen with placebo (355 ± 25 m at baseline and 349 ± 44 m at week 12). Treatment with bosentan also improved cardiopulmonary hemodynamics and functional class. Asymptomatic increases in hepatic aminotransferases were observed in two bosentan-treated patients. In a second double-blind, placebo-controlled study (the Bosentan Randomized Trial of Endothelin Antagonist Therapy for Pulmonary Hypertension-1 Study[23]), bosentan (125 or 250 mg bid) was evaluated in 213 patients with functional class III and IV PAH (either primary or associated with connective tissue disease), for a minimum of 16 weeks (62.5 mg bid for 4 weeks then target dose). Bosentan improved the 6MW distance by 36 m, whereas deterioration (– 8 m) was seen with placebo. The difference between treatment groups in the mean change in 6MW distance was 44 m in favor of bosentan (95% confidence interval, 21 to 67 m; $p = 0.0002$). The risk of clinical worsening was reduced by bosentan compared to placebo ($p = 0.0015$, log-rank test). Abnormal hepatic function test findings, syncope, and flushing occurred more frequently in the bosentan group.

Two important articles describing longer-term outcomes with bosentan therapy have been recently published. In the first, McLaughlin et al[24] found that first-line therapy with bosentan, with the subsequent addition or transition to other therapy as necessary, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months. In contrast, predicted survival rates from the National Institutes of Health Registry formula are 69% and 57%, respectively. In addition, at the end of 12 months and 24 months, 85% and 70% of patients, respectively, remained alive and receiving bosentan monotherapy. Factors that predicted a worse outcome included World Health Organization functional class IV and 6MW distance below the median (358 m) at baseline. In the second study, Sitbon et al[25] compared survival in patients with functional class III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol. Baseline factors for the 139 patients treated with bosentan and the 346 patients treated with epoprostenol suggested that the epoprostenol cohort had more severe disease. Kaplan-Meier survival estimates after 1 year and 2 years were 97% and 91%, respectively, in the bosentan cohort, and 91% and 84% in the epoprostenol cohort. Cox regression analyses adjusting for differences in baseline factors showed a greater probability of death in the epoprostenol cohort. When matched cohorts of 83 patients each were selected, survival estimates were similar. In the bosentan cohort, 87% and 75% of patients followed up for 1 year and 2 years, respectively, remained on monotherapy. No evidence was found to suggest that initial treatment with oral bosentan, followed by or with the addition of other treatment if needed, adversely affected the long-term outcome compared with initial IV epoprostenol in patients with class III IPAH.

Bosentan has also been studied in children with IPAH and PAH associated with congenital heart disease or connective tissue disease.[26] In this retrospective study,[26] 86 children started bosentan with or without concomitant IV epoprostenol or subcutaneous treprostinil therapy. At the cutoff date, 68 patients (79%) were still treated with bosentan, 13 patients (15%) had treatment discontinued, and 5 patients (6%) had died. Median exposure to bosentan was 14 months. In 90% of the patients (n = 78), functional class improved (46%) or was unchanged (44%) with bosentan treatment. PAPm and PVR decreased (64 ± 3 to 57 ± 3 mm Hg, $p = 0.005$; and 20 ± 2 to 15 ± 2 U/m^2, $p = 0.01$, respectively; n = 49 [± SEM]). Kaplan-Meier survival estimates at 1 year and 2 years were 98% and 91%, respectively.

Most recently, Galie et al[27] reported the results of a multicenter, double-blind, randomized, and placebo-controlled study of bosentan therapy in patients with functional class III Eisenmenger syndrome (Bosentan Randomized Trial of Endothelin Antagonist Therapy for Pulmonary Hypertension-5). Fifty-four patients were randomized 2:1 to bosentan (n = 37) or placebo (n = 17) for 16 weeks. The placebo-corrected effect on systemic pulse oximetry was 1.0% (95% confidence interval, − 0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced PVR index (− 472.0 dyne·s·cm^{-5}; $p = 0.0383$). PAPm decreased (− 5.5 mm Hg; $p = 0.0363$), and exercise capacity increased (53.1 m; $p = 0.0079$). Treatment was discontinued in four patients as a result of adverse events: two patients (5%) in the bosentan group, and two patients (12%) in the placebo group. Bosentan is currently approved

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by the FDA for the treatment of patients with functional class III-IV PAH.

Sitaxsentan

In the first randomized, double-blind, placebo-controlled trial[28] with sitaxsentan (an endothelin A receptor selective antagonist) in PAH (the Sitaxsentan to Relieve Impaired Exercise-1 study), 178 NYHA functional class II, III and IV patients with either IPAH, PAH related to connective tissue disease, or PAH related to congenital systemic to pulmonary shunts, sitaxsentan improved exercise capacity (6MW distance) and functional class after 12 weeks of treatment. The treatment effects in the sitaxsentan groups were 35 m ($p < 0.01$) for the 100-mg dose and 33 m ($p < 0.01$) for the 300-mg dose. NYHA functional class and cardiopulmonary hemodynamics also improved. The incidence of liver function abnormalities was more favorable for the 100-mg dose. The most frequently reported clinical adverse events with sitaxsentan treatment were headache, peripheral edema, nausea, nasal congestion, and dizziness, and the most frequently reported laboratory adverse event was increased international normalized ratio or prothrombin time related to the effect of sitaxsentan on inhibition of CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin.

A second double-blind, placebo-controlled trial with sitaxsentan in PAH (the Sitaxsentan to Relieve Impaired Exercise-2 study[29]) randomized 247 PAH patients (245 were treated) with IPAH, or PAH associated with connective tissue disease or congenital heart disease: placebo ($n = 62$); sitaxsentan, 50 mg ($n = 62$) or 100 mg ($n = 61$); or open-label bosentan (6MW tests, Borg dyspnea scores, and functional class assessments third-party blind; $n = 60$). The primary end point was change in 6MW distance from baseline to end of study. At week 18, patients treated with sitaxsentan, 100 mg, had an increased 6MW distance compared with the placebo group (31.4 m, $p = 0.03$), and an improved functional class ($p = 0.04$). The placebo-subtracted treatment effect for sitaxsentan, 50 mg, was 24.2 m ($p = 0.07$), and for open-label bosentan was 29.5 m ($p = 0.05$). The incidence of elevated hepatic transaminases (more than three times the upper limit of normal) was 6% for placebo; 5% for sitaxsentan, 50 mg; 3% for sitaxsentan, 100 mg; and 11% for bosentan. A new drug application is pending with the FDA.

Ambrisentan

An initial, phase two study[30] examined the efficacy and safety of four doses of ambrisentan, an oral endothelin type A receptor-selective antagonist, in patients with PAH. In this double-blind, dose-ranging study,[30] 64 patients with functional class II and III IPAH or PAH associated with connective tissue disease, anorexigen use, or HIV infection were randomized to receive 1, 2.5, 5, or 10 mg of ambrisentan qd for 12 weeks followed by 12 weeks of open-label ambrisentan. At 12 weeks, 6MW distance was increased (+ 36.1 m, $p < 0.0001$), with similar and statistically significant increases for each dose group (range, + 33.9 to + 38.1 m). Improvements were also observed in Borg dyspnea index, functional class, subject global assessment, PAPm (− 5.2 mm Hg, $p < 0.0001$), and cardiac index (+ 0.33 L/min/m^2, $p < 0.0008$). Adverse events were mild and unrelated to dose, including the incidence of elevated serum aminotransferase concentrations more than three times the upper limit of normal (3.1%). Two phase III clinical trials of ambrisentan in patients with PAH have recently been completed, and publication of the results is pending. Ambrisentan remains an investigational agent at this time.

Phosphodiesterase Inhibitors

Sildenafil

Sildenafil is a potent and highly specific phosphodiesterase 5 inhibitor that has been previously approved for erectile dysfunction. Several reports[31–33] of nonrandomized, single-center studies of PAH patients treated with long-term sildenafil suggested promise for sildenafil as a therapeutic agent. A double-blind, placebo-controlled study (the Sildenafil Use in Pulmonary Arterial Hypertension-1 study,[34]) randomly assigned 278 patients with symptomatic PAH (either idiopathic or associated with connective tissue disease or with repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil (20, 40, or 80 mg po tid) for 12 weeks. 6MW distance increased from baseline in all sildenafil groups; mean placebo-corrected treatment effects were 45 m (+ 13.0%), 46 m (+ 13.3%), and 50 m (+ 14.7%) for 20, 40, and 80 mg of sildenafil, respectively ($p < 0.001$ for all comparisons). All sildenafil doses reduced the PAPm, improved the functional class, and were associated with side effects such as headache, flushing, epistaxis, dyspepsia, and diarrhea. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo. Among 222 patients completing 1 year of treatment with sildenafil monotherapy, the improvement from baseline at 1 year in the 6MW was 51 m. It should be noted that long-term data for sildenafil are available only at a dose of 80 mg po tid, while the dose approved by the FDA for the treatment of PAH is 20 mg tid.

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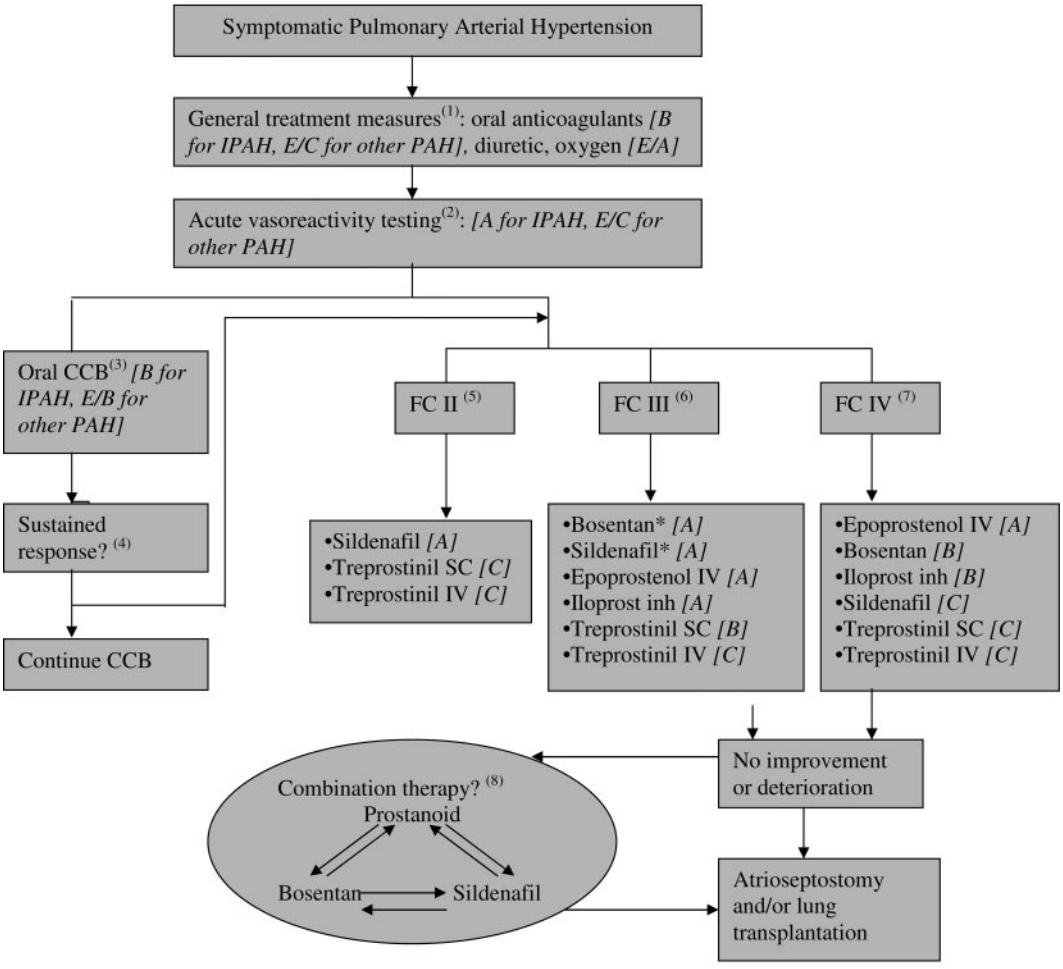

* Not in order of preference.

FIGURE 1. Treatment algorithm for PAH. The recommended therapies presented in this algorithm have been evaluated mainly in those with IPAH, or PAH associated with connective tissue disease or anorexigen use. Extrapolation to other forms of PAH should be made with caution. Country-specific regulatory agency approval status and functional class indications for PAH medications vary. *(1)* Anticoagulation should be considered for patients with IPAH, and patients with an indwelling catheter for the administration of an IV prostanoid, in the absence of contraindications. Diuretics and oxygen should be added as necessary. *(2)* A positive acute vasodilator response is defined as a fall in PAPm $\geq$ 10 mm Hg to $\leq$ 40 mm Hg, with an unchanged or increased cardiac output when challenged with inhaled nitric oxide, IV epoprostenol, or IV adenosine. *(3)* Consideration should be given to using a PAH-specific medication such as a phosphodiesterase 5 inhibitor, endothelin receptor antagonist, or prostanoid as first-line treatment instead of a CCB in patients with PAH that is not IPAH or PAH associated with anorexigen use, or in those in an advanced functional class (FC) given the exceedingly low long-term response rate to CCB monotherapy in the former and poor prognosis in the latter. *(4)* Sustained response to CCB therapy is defined as being in functional class I or II with normal or near-normal hemodynamics after several months of treatment. *(5)* The risks and benefits of treatment in early PAH should be considered. *(6)* First-line therapy for functional class III includes bosentan, sildenafil, epoprostenol, inhaled (inh) iloprost, and treprostinil (see text for details). *(7)* Most experts recommend IV epoprostenol as first-line treatment for unstable patients in functional class IV. *(8)* RCTs studying add-on combination treatment regimens are underway. Designators *[A]*, *[B]*, *[C]*, *[D]*, and *[E/A]*, *[E/C]* *[E/B]* are defined in Table 2. *Not in order of preference. SC = subcutaneous.

SUMMARY

The paradigm for treatment of PAH continues to advance rapidly. Multicenter randomized clinical trials (RCTs) have provided a basis for evidence-based practice. The treatment algorithm provided (Fig 1) attempts to summarize the current approach to therapy for PAH. The following brief overview, organized by functional class, is intended to facilitate clinical application of the algorithm. It should be noted that func-

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Table 4—*Summary of Recommendations: Update to the 2004 ACCP Guidelines***

Functional Classes	Description	Recommendations
Functional class II		
10	PAH patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with:	
a	Sildenafil	Level of evidence: good; benefit: substantial; grade of recommendation: A
b	Subcutaneous treprostinil	Level of evidence: low; benefit: small/weak; grade of recommendation: C. Although treprostinil is FDA approved for use in patients in functional class II, it would seldom be recommended in such patients due to the complexity of administration, side effects, and cost.
c	IV treprostinil	Level of evidence: low; benefit: small/weak; grade of recommendation: C. Although treprostinil is FDA approved for use in patients in functional class II, it would seldom be recommended in such patients due to the complexity of administration, side effects, and cost.
d		Data pertaining to the treatment of functional class II patients remain limited, and enrollment in clinical trials is encouraged.
Functional class III		
11	PAH patients in functional class III who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with:	
a	Endothelin receptor antagonists (bosentan), or sildenafil, in no order of preference	Level of evidence: good; benefit: substantial; grade of recommendation: A
b	IV epoprostenol	Level of evidence: good; benefit: substantial; grade of recommendation: A
c	Inhaled iloprost	Level of evidence: good; benefit: intermediate; grade of recommendation: A
d	Subcutaneous treprostinil	Level of evidence: fair; benefit: intermediate; grade of recommendation: B
e	IV treprostinil	Level of evidence; low; benefit: intermediate; grade of recommendation: C
Functional class IV		
12	PAH patients in functional class IV who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with IV epoprostenol (treatment of choice).	Level of evidence: good; benefit: substantial; grade of recommendation: A
13	Other treatments available for the treatment of functional class IV PAH patients include, in no hierarchical order:	
a	Endothelin receptor antagonists (bosentan)	Level of evidence: fair; benefit: intermediate; grade of recommendation: B
b	Inhaled iloprost	Level of evidence: fair; benefit: intermediate; grade of recommendation: B
c	Subcutaneous treprostinil	Level of evidence: fair; benefit: intermediate; grade of recommendation: B
d	Sildenafil	Level of evidence: low; benefit: intermediate; grade of recommendation: C
e	IV treprostinil	Level of evidence; low; benefit: intermediate; grade of recommendation: C

*Refer to Table 1 for recommendations that have not changed since the 2004 guidelines.

tional class is difficult to quantify, and may vary among patients and care providers. It may not always correlate with other indexes of disease severity, although it does correlate with outcome (in patients with IPAH). Accordingly, decisions regarding therapy should take into account a variety of variables, including but not limited to functional class. Treating physicians should also consider cardiopulmonary hemodynamics, 6MW distance, signs and symptoms of right-heart failure, side effect profile, and drug-drug interactions when making

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recommendations to individual patients. Cost may be a consideration in the choice of therapy.

Functional Class II

Currently, the only therapies approved for functional class II patients are sildenafil and subcutaneous and IV treprostinil. Clinical trials with sitaxsentan[28,29] and ambrisentan[30] included functional class II patients, while an ongoing trial with bosentan is studying functional class II patients. Due to the ease of administration and relative efficacy, sildenafil may be the first choice for most functional class II patients. Enrollment into clinical trials is also encouraged.

Functional Class III

There are now five drugs in three therapeutic classes approved by the FDA for the treatment of patients with functional class III PAH. Rational therapeutic decisions must be made based on the evidence outlined above, knowledge of an individual patient's specific situation, clinical judgment, and patient preferences. Most experts now consider one of the two approved oral therapies (bosentan or sildenafil, listed in no order of preference) for patients with "early" functional class III PAH. In choosing between these agents, clinicians should consider relative toxicities. For example, patients with liver abnormalities, or inability to have liver tests monitored on a monthly basis might be better served by sildenafil. Patients with ocular disease or recurrent epistaxis might be better candidates for bosentan. If cost is a consideration, sildenafil tends to be less expensive. Patients with more advanced class III disease may require treatment with a prostanoid, such as IV epoprostenol or treprostinil, inhaled iloprost, or subcutaneous treprostinil. It is anticipated that we will soon have evidence regarding the use of add-on and combination therapy. Until additional evidence becomes available, add-on or combination therapy might be considered in the context of enrollment into clinical trials.

Functional Class IV

While all currently labeled therapies are approved for functional class IV patients, based on the quality of the evidence and the net risk/benefit profile, we strongly encourage IV epoprostenol as the treatment of choice for these most critically ill patients. IV epoprostenol has a rapid and predictable onset of action, and most experts are familiar with how to titrate this drug in the acute setting. Experience with IV treprostinil is accumulating; in some instances this may be a suitable alternative to IV epoprostenol. Recognizing that limited data are available on which to base treatment choices in patients with functional class IV symptoms, oral, subcutaneous, and inhaled agents should generally not be used as first-line therapy in this situation unless the patient refuses IV therapy or is believed not to be capable of managing the complex delivery system.

Conclusions

Recommendations regarding therapy obviously need to be applied in light of the individual patient's specific situation (Table 4). The importance of a thorough diagnostic evaluation, looking for underlying causes and contributing factors, cannot be overemphasized. Educational efforts have contributed to improved recognition of PAH, facilitating earlier initiation of therapy. This should contribute to better clinical outcomes. Due to the complexity of the diagnostic evaluation required, and the treatment options available, it continues to be strongly recommended that consideration be given to referral of patients with PAH to a specialized center. Well-controlled clinical trials should continue to lead to further improvements in the treatment of this very challenging disease.

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Medical Therapy for Pulmonary Arterial Hypertension: Updated ACCP Evidence-Based Clinical Practice Guidelines

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Chest 2007;131;1917-1928
DOI 10.1378/chest.06-2674

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