Evidence-based Medical Management of Pulmonary Hypertension 2008: Review of Updated 2007 ACCP Guidelines

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During the past decade remarkable advances have been made in the understanding, diagnosis, and clinical management of pulmonary arterial hypertension (PAH). Each of these issues was carefully addressed in the American College of Chest Physicians (ACCP) guidelines document published in 2004.[1] This document described a number of new therapeutic classes, several of which were undergoing active investigation. A number of important clinical trials have since been published; and the ACCP has recently published updated recommendations on the medical management of PAH based on this new information.[2] These guidelines incorporate the latest clinical trials through September 2006, highlight newly approved therapeutic agents for PAH, and provide treatment strategies that include combination therapy. Recommendations for therapeutic strategies remain largely based on the patient's functional class. The strength of evidence utilizes the same grading system as in the 2004 ACCP guidelines for PAH.[1,2] The goal of this article is to review the important studies leading to the latest recommendations with regard to disease-specific PAH therapy, as well as to update the reader on trials published since that time.

Calcium Channel Antagonists

The utility of oral calcium channel blockers (CCBs) in PAH remains very limited. No randomized controlled trials (RCT) have studied the use of CCBs in PAH. The subsets of patients that appear to benefit from CCBs are those who have shown an acute response to vasoreactivity testing during right heart catheterization. Sitbon et al retrospectively evaluated 557 consecutive patients with idiopathic PAH who underwent acute vasodilator testing.[3] Responders were defined by a greater than 20% decrease in mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Acute responders were treated with oral CCBs and followed every 3 to 6 months. Patients were classified as long-term CCB responders if their functional class was I or II after 1 year of therapy without adding additional medications for PAH. Of the 70 acute responders to vasoreactivity testing, 38 patients remained responsive to CCBs after 1 year; and this represented less than 7% of the total cohort. The long-term CCB responders had a lower mean PAP of 33 ± 8 mmHg (± SD) at baseline compared with the CCB failure group. Given these findings, the definition of acute vasoreactivity response was redefined as a decrease in mean PAP ≥ 10 mmHg to ≤ 40 mmHg with an increased or unchanged cardiac output. This important study suggests that only a small subset of patients will benefit from oral CCBs. No major change was made to the 2007 ACCP guidelines for use of oral CCBs compared with the 2004 guidelines, as shown in **Table 1**.[1,2] Empiric CCB therapy is never recommended.

Phosphodiesterase Inhibitors

Nitric oxide stimulation of vascular endothelium increases cyclic guanosine 3'-5' monophosphate (cGMP) levels and results in vasorelaxation. Phosphodiesterase type 5 (PDE5) rapidly breaks down cGMP. In the pulmonary vasculature, PDE5 is highly expressed and its inhibition can sustain the vasodilatory effect of NO. Inhibitors of PDE5 such as sildenafil have vasodilatory effects in the pulmonary vasculature in patients with PAH.

Sildenafil has been reported to improve functional class and exercise tolerance in both observational and randomized clinical studies.[4,5] The Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study randomized 278 functional class II-IV patients with idiopathic PAH or PAH secondary to connective-tissue disease or previously repaired congenital shunts to 12 weeks of either placebo or sildenafil (20, 40, or 80 mg three times daily).[6] The sildenafil group had improvements in 6-minute walk test distance (6MWD), functional class, and mean PAP with all three dosages compared with placebo. In an open-label extension of sildenafil

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Table 1. Overview of Updated ACCP Guidelines on Medical Therapy for PAH

Recommendation	Level of Evidence	Net Benefit	Grade of Recommendation
Calcium channel blockers (CCBs)			
Acute responders to vasoreactivity testing, defined as fall in mean PAP ≥ 10 mmHg to ≤ 40 mmHg with increased or unchanged cardiac output, and absence of right heart failure may be treated with oral CCBs, with careful reassessment:			
1. Idiopathic PAH	low	substantial	B
2. Secondary PAH from underlying conditions	expert opinion	intermediate	E/B
Sildenafil			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. II or III	good	substantial	A
2. IV	low	indeterminate	C
Intravenous epoprostenol			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. III or IV	good	substantial	A
Treprostinil			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. II			
a. Subcutaneous or intravenous	low	small/weak	C
2. III or IV			
a. Subcutaneous	fair	intermediate	B (III) C (IV)
b. Intravenous	low	intermediate	C (III and IV)
Inhaled iloprost			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. III	good	intermediate	A
2. IV	fair	intermediate	B
Bosentan			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. III	good	substantial	A
2. IV	fair	intermediate	B

Strength of Recommendation Scale: A, strong; B, moderate; C, weak; D, negative; I, inconclusive; E/X, expert opinion only/consensus

at mostly 80 mg tid to one year, 86% of patients continued to receive sildenafil monotherapy and had improvements in their 6MWD. The Food and Drug Administration (FDA) subsequently approved sildenafil for treatment of PAH at a dose of 20 mg three times daily. The 2007 ACCP guideline recommendations for sildenafil therapy are shown in **Table 1** and are different from the 2004 ACCP guidelines.[1,2] It is listed as a therapy in patients with functional class II-IV PAH.[2] The majority of patients in the SUPER trial were in functional class II or III, and these patients now have the strongest evidence for benefit.[6] The updated ACCP guideline graded sildenafil data the highest quality for functional class II or III, while class IV patients received a substantially lower grade.[2]

Tadalafil is another PDE5 inhibitor reported in an observational study to benefit patients with PAH.[7] A phase 3 clinical trial recently finished enrollment.[8] Tadalafil was not discussed in the 2007 ACCP guidelines.

Prostanoids

Prostacyclin is a potent vasodilator produced in the vascular endothelium. Several methods to administer exogenous prostacyclin analogues (referred to as prostanoids) exist. Epoprostenol is an intravenous, potent, short-acting vasodilator with a half-life of 3 to 6 minutes that has been well studied in randomized trials of idiopathic PAH[9] and in patients with PAH secondary to scleroderma and found to be efficacious in both groups.[10] The long-term efficacy of intra-

Table 2. Prostanoid Studies in PAH

Trial Name	Follow-up Testing	Enrolled Patients	Drug	Change in meters for mean 6MWD from baseline			Change in mmHg in mean PAP from baseline			Change in dyne-s-cm^{-5} in mean PVR from baseline		
				Treated	Placebo	*P*	Treated	Placebo	*P*	Treated	Placebo	*P*
Randomized Trials												
Barst et al[9]	12 wk	81	IV epoprostenol	32*	-15	<.003	-4.8±1.3	1.9±1.6	<.002	-272±56	120±96	<.00
Badesch et al[10]	12 wk	111	IV epoprostenol	63.5*	-36	<.001	-5.0±1.1	0.94±1.1	NR†	-366±61	74±45	NR†
Simonneau et al[14]	12 wk	470	SC treprostinil	10‡	0	<.006	-2.3±0.5	0.7±0.6	.0002	NR	NR	NR
Olschewski et al[20]	12 wk	203	inhaled iloprost	~16§	~-20§	.004	-4.6±9.3	-0.2±6.9	<.001	-239±279	96±322	<.001
Observational Studies												
McLaughlin et al[11]	17±15mo	162	IV epoprostenol	215	NA	<.0001	-8.0¶	N/A	<.0001	-520¶	NA	<.0001
Sitbon et al[12]	3 mo	178	IV epoprostenol	125	NA	<.001	-7.0¶	NA	<.0001	NR	NR	NR
Kuhn et al[13]	1 year	49	IV epoprostenol	73\\	NA	.078	-8¶\\	NA	<.001	-528¶\\	NA	<.001
Tapson et al.[16]	12 wk	14	IV treprostinil	82	NA	.001	-4.2±1.6	NA	.03	-752±152	NA	.001
Opitz et al.[21]	12 wk	48	inhaled iloprost	NR	NR	NR	1.0¶	NA	.41	130	NA	.12

* trial compared IV epoprostenol plus conventional therapy versus conventional therapy alone
† *P* values not reported yet confidence intervals did not cross zero, thus implying statistical significance
‡ median change for 6MWD reported
§ actual values for 6MWD not reported; absolute change in 6MWD between groups was 36.4 m; values are estimated from graph for 6MWD
¶ ± values not reported for change from baseline
\\ values listed are only for the patients with idiopathic PAH, of whom only 37 underwent right heart catheterization

6MWD = 6-minute walk test distance; IV = intravenous; NA = not applicable; NR - not reported; PAP = pulmonary artery pressure; PVR= pulmonary vascular resistance; sc = subcutaneous

venous epoprostenol has been evaluated in several observational studies[11-13] of class III or IV idiopathic PAH patients (**Table 2**). Based on the RCT and observational studies, intravenous epoprostenol appears to benefit survival in functional class III and IV idiopathic PAH patients. Epoprostenol is FDA-approved for use in patients with idiopathic PAH and PAH secondary to the scleroderma spectrum of disease. The most common complication with intravenous epoprostenol remains line-related infections and possible sepsis.[9-12]

Treprostinil is another prostacyclin analogue, previously approved for subcutaneous administration and now available for intravenous therapy. It has a longer half-life (4.5 hours) than prostacyclin and its stability obviates the need for refrigeration. In a 12-week double-blind trial, 470 functional class II-IV patients with idiopathic PAH or PAH secondary to congenital systemic-to-pulmonary shunts or connective tissue disease were randomized to continuous subcutaneous treprostinil versus placebo.[14] 6MWD and mean PAP improved with treprostinil (**Table 2**). The most common adverse event was infusion site pain (85% in the treprostinil group). An open-label extension of this study followed 860 patients for 4 years.[15] Among the 15% of patients who continued to receive subcutaneous treprostinil alone, survival at 1, 2, 3, and 4 years was 88%, 79%, 73%, and 70%. Site pain was the most common adverse event (92% of patients) causing a significant number of patients to drop out.

Because of the high frequency of site pain limiting subcutaneous administration, treprostinil administered intravenously was studied in a 12-week open-label prospective trial of 16 functional class III and IV patients with idiopathic PAH and PAH due to connective tissue disease or congenital heart disease.[16] In the 14 patients who completed the trial, 6MWD, mean PAP, and PVR improved from baseline (**Table 2**). Similar results were found in an open-label trial transitioning 31 class II and III patients from intravenous epoprostenol to intravenous trepostinil.[17] The effects on quality of life are currently being evaluated in patients switched from intravenous epoprostenol to intravenous treprostinil.[18] The long-term efficacy of intravenous treprostinil in functional class II-IV patients is still being evaluated. The strength of evidence in the updated ACCP guidelines does not exceed intravenous epoprostenol in functional class III

Table 3. Endothelin Receptor Antagonist Studies in PAH

Trial Name	Follow-up Testing	Enrolled Patients	Drug	Change in meters for mean 6MWD from baseline			Change in mmHg in mean PAP from baseline			Change in dyne-s-cm^{-5} in mean PVR from baseline		
				Treated	Placebo	*P*	Treated	Placebo	*P*	Treated	Placebo	*P*
Randomized Trials												
Channick et al[23]	12 wk	32	bosentan	77	-15	.0097	-1.6±1.2	5.1±2.8	0.013	-223±56	191±74	<.001
Rubin et al[25]	16 wk	213	bosentan, combined*	36	-8	<.001	NR	NR	NR	NR	NR	NR
Galie et al[30]	12 wk	64	ambrisentan	36†	NA	<.0001	-5.2±6.3†	N/A	<0.05	-226±202†	N/A	<.05
Barst et al.[32]	12 wk	178	sitaxsentan 100 mg	22	-13	<.01	-3±8	0±8	NS	-221±422	49±244	<.001
			300 mg	20		<.01	-5±11		<0.01	-194±333		<.001
Barst et al[33]	18 wk	247	sitaxsentan 50 mg	17.8	- 6.5	.07	NR	NR	NR	NR	NR	NR
			100 mg	25		.03						
Observational Studies												
Provencher et al[27]	16 wk	‡	bosentan	42	NA	.003	-3§	NA	0.012	NR	NR	NR

* data for 6MWD are for combined bosentan group, which included patients receiving 125 mg or 250 mg twice daily
† reported values are for four combined doses of ambrisentan
‡ 99 patients had 6MWD testing at 16 weeks; 73 patients had right heart catheterization measurements
§ ± values not reported for change from baseline

6MWD = 6-minute walk test distance; NA = not applicable; NR = not reported; NS = not significant; PAP= pulmonary artery pressure; PVR = pulmonary vascular resistance

or IV patients, as shown in **Table 1**. The subcutaneous form has been given a higher evidence grade than the intravenous form.[2] A new inhaled form of treprostinil currently being investigated was not discussed.[19]

Iloprost is a prostacyclin analogue with a half-life of 25 minutes available in intravenous, subcutaneous, and inhaled forms. The last has been studied the most extensively. A 12-week trial randomized 203 functional class III or IV patients with idiopathic PAH or PAH associated with appetite suppressants, chronic thromboembolic disease, or connective tissue disease to inhaled iloprost or placebo.[20] The primary endpoint, defined as a ≥10% improvement in 6MWD and an improvement in functional class, was reached in 16.8% of patients in the iloprost group compared with 4.9% in the placebo group. Improvements in 6MWD, mean PAP, and PVR were also seen (**Table 2**). In a prospective open-label study of 76 functional class II-IV patients with idiopathic PAH, only a minority of patients could be stabilized with inhaled iloprost monotherapy during a follow-up period of up to 5 years.[21] In general, inhaled iloprost appears to be an effective treatment in patients with functional class III and IV PAH but, as with oral agents, it was not recommended as first-line therapy in class IV patients. For inhaled iloprost, the strength of evidence in the 2007 ACCP guidelines is slightly higher compared with the 2004 recommendation (**Table 1**).[1,2]

Endothelin Receptor Antagonists

Patients with PAH have increased lung expression of endothelin-1 (ET-1) and blood levels have been correlated with disease severity.[22] ET-1is a potent vasoconstrictor and may contribute to smooth muscle hypertrophy. Endothelin receptor antagonists are designed to halt the effects of ET-1 and offer another pharmacologic class for the treatment of PAH.

Bosentan was the first oral endothelin receptor antagonist studied in PAH. A double-blind, placebo-controlled study of 32 class III or IV patients with idiopathic PAH or PAH associated with scleroderma demonstrated significant improvement in 6MWD, PAP, and PVR at 12 weeks (**Table 3**).[23] An open-label observational study involving 29 of the original 32 patients demonstrated persistent improvements in 6MWD, PVR, and functional class.[24]

The Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) randomized 213 functional class III or IV patients with idiopathic PAH or PAH associated with connective tissue disease to placebo or bosentan.[25] At 16 weeks, 6MWD improved with bosentan (**Table 3**). Functional class improved to II in 38% of patients receiving 250 mg.

McLaughlin et al examined the long-term efficacy of bosentan in a paper combining two placebo-controlled trials.[26] Survival at 1 and 2 years was 96.4% and 88.5%, compared with predicted survival of 69.2% and 57.3% without targeted therapy. Of the patients who were alive at 1 and 2 years, 78% and 55% were receiving bosentan monotherapy. The most common adverse effect was elevated hepatic transaminases at more than three times the upper limit of normal in 14.9% of patients.

A retrospective analysis of 103 consecutive patients of functional class III or IV idiopathic PAH treated with bosen-

tan showed improvements in 6MWD and PAP at 16 weeks (**Table 3**).[27] After 24 ± 15 months, prostanoid therapy had been initiated in 44% of patients. Survival at 1 and 2 years was 90% and 87%, compared with predicted survival without targeted therapy of 63% and 45%. Long-term survival was assessed in a cohort of 139 functional class III patients with idiopathic PAH treated with bosentan therapy and compared with 346 historical controls treated with intravenous epoprostenol.[28] Survival for the bosentan cohort was 97% and 91% at 1 and 2 years, compared with 91% and 84% in the epoprostenol cohort.

A European study randomized 185 functional class II patients to bosentan or placebo for 6 months.[29] A significant 23% reduction in mean PVR was seen, as well as a trend toward improvement in 6MWD. Death, hospitalization, or symptomatic progression was significantly delayed with bosentan (3% vs 11% with placebo). This study has not been formally subjected to peer review. The updated ACCP guideline recommendations regarding bosentan are shown in **Table 1** and did not change from the previous guidelines, finding bosentan's most evidence-based role in monotherapy for class III patients.[1,2]

Ambrisentan is a second endothelin receptor antagonist recently approved for treatment of PAH. However, publication of the pivotal clinical trials and its subsequent FDA approval had not occurred before the final drafting of the 2007 ACCP guidelines. Ambrisentan was discussed in the guideline text based on a single available clinical trial of 64 functional class II or III patients with idiopathic PAH or PAH associated with connective tissue disease, anorexigen use, or HIV infection, where improvements in functional class, 6MWD, mean PAP, and PVR after 12 weeks of therapy appeared promising (**Table 3**).[30] Long-term efficacy of ambrisentan from continuation studies was also not available before the 2007 guidelines were finalized.[31] Ambrisentan was listed as an investigational agent in the 2007 ACCP guidelines.[2] Broadly interpreting the Summary of Recommendations in the guidelines, ambrisentan could be considered as an alternative endothelin receptor antagonist for patients with functional class III PAH.

Sitaxsentan is an endothelin receptor antagonist that has not yet been approved for treatment of PAH in the United States, though it has been approved in other countries. However, publication of the pivotal clinical trials and regulatory approval outside the United States had not occurred before the final drafting of the 2007 ACCP guidelines. Sitaxsentan was discussed in the guideline text based on available clinical trials. The first was a randomized study of 178 functional class II and III patients with idiopathic PAH or PAH secondary to connective tissue disease or congenital heart disease receiving 12 weeks of placebo or sitaxsentan (STRIDE-1).[32] The second was a trial of 247 functional class II-IV patients with idiopathic PAH or PAH secondary to connective tissue disease or congenital heart disease who were randomized to receive placebo, two different sitaxsentan doses, or open-label bosentan (STRIDE-2).[33] At 18 weeks, 6MWD improved in all treatment groups (**Table 3**). Functional class improved or was unchanged in 98% of patients receiving 100 mg sitaxsentan, compared with 87% of patients receiving placebo, yet no difference was seen with the 50 mg sitaxsentan group or open-label bosentan compared with placebo.[34] A recent trial examining sitaxsentan benefit and tolerance in patients who discontinued bosentan because of hepatotoxicity was also not available for review by the time of guideline submission. Since it was only in clinical trials at the time of review, there were no ACCP guideline recommendations on the use of sitaxsentan.

Future Directions in Medical Management

The 2007 ACCP guidelines on the medical management of PAH are largely based on trials that studied the various agents as monotherapies.[2] The medical management of PAH worldwide is fast-moving and is often quite different among practitioners from the functional class-based approach using only pre-2007 approved drugs that is emphasized in the ACCP guidelines. The guidelines are most important in determining which pharmacologic class is the best option for initial therapy, yet many patients may need additional therapies to halt the progressive nature of PAH. Combination therapy for PAH is an important and exciting area of current research for the management of PAH, and is reviewed elsewhere in this issue of *Advances in Pulmonary Hypertension.*

ACCP Treatment Algorithm

The ACCP provided a treatment algorithm for PAH in the 2007 ACCP guidelines. As medical management in PAH is shifting in some regions toward initiation of therapy in less symptomatic patients, and toward early combination therapy,[35] this paradigm was acknowledged in the treatment algorithm as a consideration.

Conclusions

PAH is a progressive disorder that carries a poor prognosis without pharmacologic intervention. The pace at which the medical therapies for PAH are evolving is rapid. Since the 2007 revision of the ACCP guidelines, several important trials have already been published that will shape future guidelines. Although the medical management of PAH may be shifting toward combination therapy, a large gap of knowledge exists regarding the efficacy and safety of combination therapy, including drug interactions. The costs associated with advanced therapeutic treatment strategies should also be carefully assessed, but were not assessed in either the 2004 or the 2007 ACCP treatment guidelines. Further studies on medical therapies for nonidiopathic PAH are also needed. Using specific treatment goals to guide therapeutic decision-making may be the most rational approach in today's PAH practice. The advances in medical therapies for PAH outlined by the 2007 ACCP guidelines offer an exciting opportunity for physicians to employ evidence-based medicine in a manner that will improve quality of life and survival for PAH patients. ■

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