Medical Therapy For Pulmonary Arterial Hypertension*

ACCP Evidence-Based Clinical Practice Guidelines

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Pulmonary arterial hypertension (PAH) is often difficult to diagnose and challenging to treat. Untreated, it is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and death. The past decade has seen remarkable improvements in therapy, driven largely by the conduct of randomized controlled trials. Still, the selection of most appropriate therapy is complex, and requires familiarity with the disease process, evidence from treatment trials, complicated drug delivery systems, dosing regimens, side effects, and complications. This chapter will provide evidence-based treatment recommendations for physicians involved in the care of these complex patients. Due to the complexity of the diagnostic evaluation required, and the treatment options available, it is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. *(CHEST 2004; 126:35S–62S)*

Historically, medical treatment of pulmonary arterial hypertension (PAH) has been difficult. Idiopathic PAH (IPAH), formerly known as primary pulmonary hypertension (PPH), carried a very poor prognosis (median survival of approximately 2.8 years from the date of diagnosis) through the mid-1980s. Since then, a number of therapeutic options have been developed, with varying degrees of evidence to support

their use. This chapter will review the current treatment of PAH, objectively detailing the evidence available to support each form of therapy. Some widely used therapies for PAH are generally accepted as being important and efficacious, although not supported by randomized controlled clinical trials (RCTs). Examples include supplemental oxygen, diuretics, oral vasodilators/calcium-channel blockers (CCBs), anticoagulation with warfarin, and digitalis. Other therapies are supported by RCTs and are approved by the US Food and Drug Administration (FDA) for the treatment of various patient groups. Such agents include epoprostenol, treprostinil, and bosentan. Still other agents are currently undergoing RCTs in PAH, including sitaxsentan, ambrisentan, sildenafil, and inhaled iloprost. This chapter will be organized as follows: a general overview of the approach to the patient with PAH; review of the evidence supporting the use of available drugs, organized by therapeutic class, with evidence-based, graded recommendations following

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each section; discussion of the future potential of combination or multimodality therapy; consideration of special situations, including children, pregnancy, porto-pulmonary hypertension, and HIV disease; and finally a summary of all graded recommendations. It is important to note that the specific recommendations provided are layered on top of general patient-care measures discussed in the text.

Methodologically, a computerized search of the MEDLINE bibliographic database from 1992 to October 2002 (see Methods chapter, page 11S) was conducted using the term *hypertension, pulmonary*. While the background provided in some sections includes selected information from basic and animal studies, the formal search was limited to articles concerning human subjects that were published in the English language and accompanied by an abstract. In addition, we searched the reference lists of included studies, practice guidelines, systematic reviews, and meta-analyses, and clinical experts identified relevant studies missed by the search strategy or published before 1992. We selected studies of oxygen, diuretics, inotropic agents (digoxin), anticoagulants, calcium antagonists, angiotensin-converting enzyme inhibitors, prostanoids (*eg*, epoprostenol, treprostinil, inhaled iloprost), L-arginine, endothelin-receptor antagonists (*eg*, bosentan, sitaxsentan, ambrisentan), phosphodiesterase-5 inhibitors (sildenafil), nitric oxide (NO), and thromboxane inhibitors (*eg*, terbogrel). We considered studies conducted among patients with known or suspected IPAH or PAH occurring in association with underlying collagen vascular disease, congenital heart disease, or chronic thromboembolic disease. 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. The summary evidence tables can be viewed on-line at http://www.chestjournal.org/content/vol126/1_suppl/.

Overview of the Approach to the Patient With PAH

The treatment of PAH begins with a thorough evaluation seeking underlying causes and contributing factors. The diagnosis of PAH is thoroughly discussed in Chapter 2. Initial therapy may be directed at the underlying cause or contributing factor, with examples including supplemental oxygen for hypoxemia, continuous positive airway pressure therapy and supplemental oxygen for obstructive sleep apnea, anticoagulation, and consideration of pulmonary thromboendarterectomy for PAH due to chronic-recurrent thromboembolic disease, etc. The identification and treatment of underlying/associated disorders can have an important effect on the success of therapy.

Following the identification of underlying associated disorders and contributing factors, specific therapy for PAH should be considered. Recognition that there is some similarity across subgroups of patients, in terms of hemodynamic and functional response to therapy (though not necessarily survival), has lead to the development of similar treatment strategies. Exceptions do, of course, exist for special situations, some of which will be addressed separately near the end of this chapter.

General Care

Vasodilator Testing

Patients with IPAH who respond to vasodilators acutely have an improved survival with the long-term use of a CCB. As such, testing of vasoreactivity is an important part of the evaluation of any patient with PAH. Over the years, investigators have used a number of agents to acutely test vasodilator responsiveness, and have used various definitions of a response including reductions in either pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), or both. These different definitions of a response have made it difficult to systematically evaluate the literature. More recently, the European Society of Cardiology formulated a consensus definition of a positive acute vasodilator response in a patient with IPAH. This was defined as a fall of mean PAP (mPAP) of at least 10 mm Hg to $\leq$ 40 mm Hg, with an increase or unchanged cardiac output (CO). It should be noted, however, that the precise definition of a favorable acute response to vasodilator is still somewhat controversial.

Although initially IV vasodilators including isoproterenol and hydralazine were used to assess vasodilator responsiveness, the use of oral CCBs came into favor in the early 1990s. In 1992, Rich et al[1] studied 64 patients with IPAH with oral nifedipine (20 mg), or diltiazem (60 mg) if they had a resting tachycardia, and the doses were repeated every hour until either a favorable response was achieved or intolerable side effects developed. In this series,[1] a favorable response was defined as a > 20% reduction in mPAP and PVR. Seventeen of the 64 patients (26.5%) were considered responders, and were subsequently treated with high-dose, oral CCBs. This group had a 94% 5-year survival. However, acute testing with oral CCBs can result in deterioration in patients who are not responsive, and this can be exacerbated by the long half-life of these agents. After several case reports of fatal outcomes associated with testing patients with

IPAH and CCBs, interest developed in the use of shorter-acting vasodilators to assess vasoreactivity prior to institution of CCBs.

In 1993, Groves et al[2] studied the acute response to IV epoprostenol in 44 patients with IPAH. An initial dose of 1 ng/kg/min was administered and increased by 1 to 2 ng/kg/min every 5 to 15 min to a maximum dose of 12 ng/kg/min. The mean tolerated dose was 8.0 ng/kg/min. The mean hemodynamic effects of epoprostenol included a 14% increase in heart rate, 5% decrease in mPAP, 47% increase in CO, and 32% decrease in PVR. Using the definition of a favorable response as > 30% decrease in PVR and > 10% decrease in mPAP, 13 of 44 patients with IPAH (30%) were considered responders. The acute response to IV epoprostenol was predictive of subsequent response to oral CCB therapy. Similarly, in a study of 35 consecutive patients with IPAH, Sitbon et al[3] evaluated the acute vasodilator response to IV epoprostenol at a starting dose of 2.5 ng/kg/min increased stepwise by increments of 2.5 ng/kg/min every 10 min to a maximal dose of 10 ng/kg/min. Using the definition of a response as a reduction of > 30% in total pulmonary resistance, 13 of 35 patients (37%) were considered responders.

IV adenosine has been shown to be a potent vasodilator through its actions on specific vascular receptors. Adenosine produces coronary vasodilatation, decreases systemic vascular resistance, and causes relaxation of smooth muscles including pulmonary arteries. Because of its short serum half-life, adenosine is a desirable agent to use as a vasodilator in the assessment of PH. Shrader et al[4] studied 15 patients (11 patients with IPAH) with IV adenosine administered at a dose of 50 μg/kg/min and increased by 50 μg/kg/min every 2 min to a maximum dose of 500 μg/kg/min to acutely assess vasodilator response. Subsequently, patients were administered hourly doses of nifedipine to assess vasodilator response. Importantly, the correlation of PVR reduction with both agents was high ($R = 0.714$; $p = 0.01$). The three patients who did not respond to adenosine also did not respond to nifedipine.

Because both IV epoprostenol and IV adenosine have the potential to cause a reduction in systemic vascular resistance and systemic hypotension, more pulmonary selective vasodilators have been sought. In 1998, Sitbon et al[5] reported the results of inhaled NO testing (10 ppm) via face mask in 33 patients with IPAH. A significant acute vasodilator response was defined by a fall in both mPAP and total pulmonary resistance of > 20%. Ten of the 33 patients responded acutely to NO, 9 of whom responded acutely to CCBs without any complications. Of the other 23 patients who failed to respond to NO, none had a response to CCBs. Notably, there were nine serious adverse events associated with the administration of CCBs in the patients not responsive to NO. This led to the conclusion that acute vasodilator testing with NO is safer than testing with CCBs. Similarly, in 1998, Ricciardi et al[5a] reported results of acute testing with NO in 17 patients with IPAH prior to undergoing a trial with nifedipine. Patients were considered responders if they had a > 20% decrease in mPAP or a > 20% decrease in PVR. Seven of the 17 patients responded to NO, while 8 of the 17 patients responded to nifedipine. There were three adverse events, including one death during challenge with nifedipine. All responders to NO responded to nifedipine, while 9 of the 10 NO nonresponders were also nifedipine nonresponders. There was a highly significant correlation between the effects of NO and nifedipine on PVR ($R = 0.67$, $p = 0.003$). More limited data exist for the use of inhaled iloprost as an acute vasoreactivity testing agent. In a recent study, Opitz et al[6] compared the response of oxygen inhalation, iloprost inhalation, IV epoprostenol, and IV iloprost. IV iloprost and epoprostenol had very similar hemodynamic profiles in terms of reduction in PVR and PAP. Inhaled iloprost exerted a selective pulmonary dilatation, resulting in a reduction of PVR and PAP without systemic vasodilatation. This study suggested that inhaled iloprost should be equivalent to IV epoprostenol and inhaled NO in terms of predicting response to CCBs.

The primary objective of acute vasodilator testing in patients with IPAH is to delineate the subset of patients who might effectively be treated with oral CCBs. As such, unstable patients or those with severe right-heart failure, who should not be treated with CCBs, need not undergo vasodilator testing. The weight of the evidence favors either IV epoprostenol or inhaled NO as preferred agents for vasodilator testing. IV adenosine may be used if neither of the other agents are available. Testing with a short-acting agent should always take place before testing with oral CCBs, given the potential complications of vasoreactivity testing with CCBs. Only those patients who have had a substantial reduction in both PAP and PVR with an acute vasodilator should undergo further testing with CCBs. Vasodilator testing is best described in the setting of IPAH. The literature does, however, suggest that the pediatric population has a higher response rate to acute vasodilators. Rates of responsiveness in patients with collagen vascular diseases have been low when tested with inhaled NO.

Calcium-Channel Antagonists/Blockers

Smooth-muscle cell hypertrophy and vasoconstriction have long been known to contribute to the pathogenesis of IPAH. More recently, abnormalities

of the voltage-gated 1.5 potassium channels have been demonstrated in IPAH. Many vasodilators have been studied in the setting of PAH. The most notable and successful of these have been the CCBs. These agents have been studied for IPAH since the mid-1980s.

As discussed above in the section on "Vasodilator Testing," in 1992 Rich et al[1] reported the results of a prospective but not randomized trial of high-dose CCBs in patients with IPAH. Patients were included in this prospective, single-center study if they had IPAH and were not too ill for a cardiac catheterization and vasoreactivity testing. The patients who had a favorable acute response were treated with high-dose CCBs for up to 5 years. The 1-, 3-, and 5-year survival was 94%, 94%, and 94% in the patients treated with CCBs compared to 68%, 47%, and 38% in those who were classified as nonresponders, a statistically significant improvement. When compared to patients enrolled in the National Institutes of Health Registry, their survival was also significantly better.

In 1993, Ogata et al[7] reported the results of an uncontrolled, retrospective, open-label, single-center study in which a combination of anticoagulant and vasodilator therapy was evaluated in patients with IPAH. Seven patients were treated with the anticoagulant warfarin combined with a vasodilator: three patients with isoproterenol, and four patients with nifedipine. The remaining 13 patients were not treated and constituted the control group. The 5-year survival was significantly higher in the group treated with anticoagulants and vasodilators: 57% vs 15%.

There has not been an RCT of oral CCBs for IPAH, nor have there been any substantial reports of success with CCBs for other forms of PAH. Based on the available data, it would be prudent to test patients with PAH with an acute vasodilator such as prostacyclin, NO, or adenosine. Patients who demonstrate a significant response to the acute administration of a short-acting vasodilator (see above) should be treated cautiously with oral CCBs, and monitored closely to determine both the efficacy and safety of such therapy. CCBs with a significant negative inotropic effect, such as verapamil, should be avoided. Nifedipine, diltiazem, or amlodipine are used most frequently, with the choice often based on the heart rate at baseline (relative bradycardia favoring nifedipine, and relative tachycardia favoring diltiazem). While early recommendations seemed to favor relatively high doses of CCBs, most experts now seem to introduce these agents more cautiously, and gradually titrate the dose as tolerated.

Warfarin, Supplemental Oxygen, Diuretics, Digoxin

In situ microscopic thrombosis has been documented in some patients with IPAH. In addition, patients with right ventricular failure and resultant venous stasis are likely at increased risk for pulmonary thromboembolism. Improved survival has been reported with oral anticoagulation in patients with IPAH.[1,8] The target international normalized ratio (INR) in patients with IPAH treated with warfarin is approximately 1.5 to 2.5, but this varies somewhat from center to center. Anticoagulation of patients with PAH occurring in association with other underlying processes, such as scleroderma or congenital heart disease, is controversial. Some experts extrapolate the evidence supporting anticoagulation in patients with IPAH to other patients with PAH, while others may not. When deciding whether or not to anticoagulate patients with PAH occurring in association with underlying processes, the risk/benefit ratio should be carefully considered. It is generally thought that the risk of GI bleeding may be higher in patients with PAH occurring in association with scleroderma. Patients with PAH occurring in association with congenital heart disease may be at some increased risk of hemoptysis. However, patients with significant right-to-left intracardiac shunting may be at increased for paradoxical embolism to the CNS. Patients with portopulmonary hypertension may be at increased risk for GI bleeding due to the presence of varices. Generally, patients with PAH receiving therapy with long-term IV epoprostenol are anticoagulated in the absence of contraindications, due in part to the additional risk of catheter-associated thrombosis.

Hypoxemia is a potent pulmonary vasoconstrictor, and can contribute to the development and/or progression of PAH. It is generally considered important to maintain oxygen saturations at $> 90\%$ at all times. This may be difficult in patients with concomitant intrinsic lung disease, or right-to-left intracardiac shunting. The use of supplemental oxygen may be somewhat more controversial in patients with large right-to-left shunts due to congenital heart disease with Eisenmenger physiology, but may help to decrease the need for phlebotomy, and potentially reduce the incidence of neurologic dysfunction and complications.

Diuretics are indicated in patients with evidence of right ventricular failure (*ie*, peripheral edema and/or ascites). Maintaining near-normal intravascular volume with diuretics, and careful dietary restriction of sodium and fluid intake is generally considered to be important in the long-term management of patients with IPAH. However, rapid and excessive diuresis may lead to systemic hypotension, renal

insufficiency, and syncope. Serum electrolytes and indices of renal function should be followed closely in patients receiving diuretic therapy.

Although not extensively studied in PAH, digitalis is sometimes utilized in patients with refractory right ventricular failure and/or atrial dysrrhythmias. Drug levels must be followed closely, especially in patients with impaired renal function.

Prevention and Treatment of Respiratory Tract Infections

Due to the potentially devastating effects of respiratory tract infections in patients with PAH, they should be immunized against influenza and pneumococcal pneumonia per the usual standards for patients with serious cardiopulmonary disease. If respiratory tract infections do develop, they should be treated aggressively.

Recommendations

1. **Patients with IPAH should undergo acute vasoreactivity testing using a short-acting agent such as IV epoprostenol or adenosine, or inhaled NO.** 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 mPAP of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or unchanged CO), should be considered candidates for a trial of 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 mPAP of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or un-**

changed CO), 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; recommendation: E/C.
9. **In patients with PAH, supplemental oxygen should be used as necessary to maintain oxygen saturations > 90% at all times.** Level of evidence: expert opinion; benefit: substantial; recommendation: E/A.

PROSTANOIDS

Introduction/Rationale

Prostacyclin is a metabolite of arachidonic acid produced primarily in vascular endothelium. It is a potent vasodilator, affecting both the pulmonary and systemic circulations. It also has antiplatelet aggregatory effects, and the pathology of the disease may include microscopic *in situ* thromboses. There is evidence to suggest that a relative deficiency of prostacyclin may contribute to the pathogenesis of PAH. In a landmark study, Christman et al[9] reported a deficiency of prostacyclin and excess of thromboxane in PAH. More recently, Tuder et al[10] showed decreased expression of prostacyclin synthase in lungs from patients with severe PAH. Clinical studies have investigated the possibility that chronic therapy with exogenous prostacyclin analogues might be of long-term benefit to patients with moderately severe to severe PAH.

Epoprostenol

In a 12-week, prospective, multicenter, randomized, controlled, open-label trial,[11] continuously IV infused epoprostenol plus conventional therapy (oral vasodilators, anticoagulation, etc) was compared to conventional therapy alone in 81 patients with severe IPAH (New York Heart Association [NYHA] func-

tional class III or IV). Exercise capacity improved in the 41 patients treated with epoprostenol (median distance walked in 6 min of 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). Indices of the quality of life were improved in the epoprostenol group (p < 0.01). Hemodynamics improved at 12 weeks in the epoprostenol-treated group; the changes in mPAP for the epoprostenol group and control group were − 8% and + 3%, respectively (difference in mean change, − 6.7 mm Hg; 95% confidence interval [CI], − 10.7 to − 2.6 mm Hg; p < 0.002), and the mean changes in PVR for the epoprostenol and control groups were − 21% and + 9%, respectively (difference in mean change, − 4.9 mm Hg/L/min; 95% CI, − 7.6 to − 2.3 mm Hg/L/min; p < 0.001). Eight patients died during the study, all of whom had received conventional therapy (p = 0.003). Serious complications included four episodes of catheter-related sepsis and one thrombotic event. It was concluded that, as compared with conventional therapy, continuous IV infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe IPAH.

A multicenter, randomized, controlled, open-label study of long-term IV epoprostenol showed improvement in exercise capacity and hemodynamics in patients with PAH occurring in association with the scleroderma spectrum of disease.[12] Epoprostenol plus conventional therapy was compared to conventional therapy alone. The primary outcome measure was exercise capacity. Other measures were cardiopulmonary hemodynamics, signs and symptoms of PH and scleroderma, and survival. Exercise capacity improved with epoprostenol (median distance walked in 6 min, 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% CI, 55.2 to 180.0 m; p < 0.001). Hemodynamics improved at 12 weeks with epoprostenol therapy. The changes in mPAP for the epoprostenol and conventional therapy groups were − 5.0 and 0.9 mm Hg, respectively (difference, − 6.0 mm Hg; 95% CI, − 9.0 to − 3.0 mm Hg), and the mean changes in PVR were − 4.6 mm Hg/L/min and 0.9 mm Hg/L/min, respectively (difference, − 5.5 mm Hg/L/min; 95% CI, − 7.3 to − 3.7 mm Hg/L/min). Twenty-one patients treated with epoprostenol, and no patients receiving conventional therapy, showed improved NYHA functional class. Borg dyspnea scores and dyspnea-fatigue ratings improved in the epoproste-

nol group. Trends toward greater improvement in severity of the Raynaud phenomenon and fewer new digital ulcers were seen in the epoprostenol group. Four patients in the epoprostenol group and five patients in the conventional therapy group died (p value not significant). Side effects of epoprostenol therapy included jaw pain, nausea, and anorexia. Adverse events related to the epoprostenol delivery system included sepsis, cellulitis, hemorrhage, and pneumothorax (4% incidence for each condition). It was concluded that continuous epoprostenol therapy improves exercise capacity and cardiopulmonary hemodynamics in patients with PAH due to the scleroderma spectrum of disease.

Epoprostenol therapy is complicated by the need for continuous IV infusion. The drug is unstable at room temperature, and is generally best kept cold prior to and during infusion (necessitating the use of ice packs). It has a very short half-life in the blood stream (< 6 min), is unstable at acidic pH, and cannot be taken orally. Due to the short half-life, the risk of rebound worsening with abrupt/inadvertent interruption of the infusion (see below), and its effects on peripheral veins, it should be administered through an indwelling central venous catheter. Due to the long duration of therapy, and the ongoing risk of catheter-associated infection, tunneled central venous catheters are generally preferred. Patients are typically begun on a very low dosage of epoprostenol (1 to 2 ng/kg/min), and the dose is gradually titrated upward in increments of 1 to 2 ng/kg/min, based on side effects and tolerance. Many patients seem to eventually reach a "plateau" dose, and may not require continued uptitration from that point. While this dose may be between 20 ng/kg/min and 40 ng/kg/min for many patients, the dose range tends to be quite wide, with considerable interindividual variability.

Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial mastication, diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal aches and pain (predominantly involving the legs and feet). These tend to be dose dependent, and often respond to a cautious reduction in dose. Severe side effects can occur with overdosage of the drug. Acutely, overdosage can lead to systemic hypotension. Long-term overdosage can lead to the development of a hyperdynamic state and high-output cardiac failure.[13]

Abrupt or inadvertent interruption of the epoprostenol infusion should be avoided, as this may, in some patients, lead to a rebound worsening of their PH with symptomatic deterioration and perhaps even death. Patients with severe disease, who are highly dependent on the hemodynamic effects of the drug, can experience clinical deterioration in a rela-

tively short period of time (20 to 30 min) with abrupt interruption of the infusion. Patients are advised to always carry with them a spare cassette of premixed epoprostenol, as well as a spare infusion pump. If central venous access is lost for whatever reason (clogging or dislodgement of the catheter), patients are generally advised to access the emergency medical system immediately. The infusion is then re-established with placement of peripheral IV access, until central venous access can be restored. Patients should generally remain within the medical system until stable central venous access has been secured.

Other complications of long-term IV therapy with epoprostenol include line-related infections (which can range from small exit site reactions, to tunnel infections and cellulitis, to bacteremic infections with sepsis), catheter-associated venous thrombosis, thrombocytopenia, and ascites. Central venous catheter placement can occasionally be associated with the development of pneumothorax or hemothorax.

Due to the complexity of administration of epoprostenol (long-term indwelling catheters, reconstitution of the drug, operation of the infusion pump, etc), strong consideration should be given to referring patients to centers of excellence in PH. Management of patients receiving long-term epoprostenol therapy requires a considerable infrastructure, including experienced nurses and physicians.

It has become more challenging to predict prognosis in the era of epoprostenol therapy. Some patients who might previously have been considered to have a poor prognosis can now enjoy relatively long-term survival receiving long-term IV epoprostenol therapy. The beneficial effects of epoprostenol therapy appear to be sustained for years in many patients with IPAH. Barst et al[14] reported long-term benefit in a small group of patients from several centers involved in the earliest clinical usage of epoprostenol. More recently, Shapiro et al[15] and McLaughlin et al[16] described sustained benefit in larger numbers of patients with continuously infused epoprostenol. It appears as though decreases in mPAP and PVR, and improvement in CO can be sustained over a period of years in many patients.

Most recently, McLaughlin et al[17] reported long-term epoprostenol therapy in 162 consecutive patients with IPAH followed up for a mean of 36.3 months (median, 31 months). Data obtained included functional class, exercise tolerance, and hemodynamics. Observed survival with epoprostenol therapy at 1 year, 2 years, and 3 years was 87.8%, 76.3%, and 62.8%, and was significantly greater than the expected survival of 58.9%, 46.3%, and 35.4% based on historical data. Baseline predictors of survival included exercise tolerance, functional class, right atrial pressure, and vasodilator response to adenosine. Predictors of survival after the first year of therapy included functional class and improvement in exercise tolerance, cardiac index, and mPAP. Similarly, Sitbon et al[18] sought to determine the factors associated with long-term survival in patients with IPAH treated with continuous epoprostenol infusion. They began with the concept that epoprostenol generally improves survival in patients with IPAH in NYHA functional class III or IV, but some patients do not benefit and must be considered for lung transplantation. The best timing for listing these patients for lung transplantation is unknown. Between December 1992 and January 2001, 178 patients with IPAH in NYHA functional class III or IV were treated with epoprostenol. The 6-min walk test and right-sided heart catheterization were performed at baseline, after 3 months receiving epoprostenol, and thereafter once a year. Overall survival rates at 1 year, 2 years, 3 years, and 5 years were 85%, 70%, 63%, and 55%, respectively. On univariate analysis, the baseline variables associated with a poor outcome were a history of right-sided heart failure, NYHA functional class IV, 6-min walk test ≤ 250 m (median value), right atrial pressure ≥ 12 mm Hg, and mPAP ≤ 65 mm Hg. On multivariate analysis, including both baseline variables and those measured after 3 months receiving epoprostenol, a history of right-sided heart failure, persistence of NYHA functional class III or IV at 3 months, and the absence of a fall in total pulmonary resistance of ≥ 30%, relative to baseline, were associated with poor survival. They concluded that survival of patients with IPAH treated with epoprostenol depends on the severity at baseline, as well as the 3-month response to therapy. They inferred that the findings suggest lung transplantation should be considered in a subset of patients who remain in NYHA functional class III or IV, or in those who cannot achieve significant hemodynamic improvement after 3 months of epoprostenol therapy, or both.

In summary, long-term IV epoprostenol therapy has had a dramatic effect on the treatment of patients with moderately severe to severe PAH. It has been studied most thoroughly in patients with IPAH and PAH occurring in association with the scleroderma spectrum of disease. Due to the requirement for constant IV infusion, it is complicated therapy, and it is strongly recommended that patients be referred to clinical centers of excellence.

Treprostinil

The success of epoprostenol therapy, coupled with the limitations of its delivery system, has led to the development of prostacyclin analogues with alternative routes of delivery. Treprostinil is a prostacyclin

analog with a half-life of 3 h. The drug is stable at room temperature. To test the hypothesis that the hemodynamic effects of treprostinil are similar to those of epoprostenol, 14 patients with IPAH were tested acutely with IV epoprostenol and then IV treprostinil.[19] The two drugs had similar effects on hemodynamics. There was a 22% reduction in PVR with epoprostenol vs a 20% reduction in PVR with treprostinil. To test the subcutaneous delivery method, the effects of IV and subcutaneous treprostinil were compared in 25 patients with IPAH. In the IV treprostinil and subcutaneous treprostinil groups, there were 6% and 13% declines in mPAP, and 23% and 28% declines in PVR, respectively. Having demonstrated that the drug favorably affects cardiopulmonary hemodynamics when administered subcutaneously acutely, an 8-week, placebo-controlled, 2:1, randomized trial of subcutaneous treprostinil was performed. Twenty-six patients with IPAH were enrolled. Two patients in the treprostinil group did not complete the study due to intolerable side effects. The remaining 15 patients were receiving a mean dose of 13.0 ± 3.1 ng/kg/min of treprostinil, while the 9 patients receiving placebo were receiving 38.9 ± 6.7 ng/kg/min at the end of the 8-week period ($\pm$ SE). There was an improvement of 37 ± 17 m in the 6-min walk distance in patients receiving the active therapy (from 373 to 411 m), compared to a 6 ± 28 m reduction in those receiving placebo (379 m vs 384 m), a nonstatistically significant trend. There was also a favorable, but nonstatistically significant trend in hemodynamic improvement, with a 20% reduction in PVR index over the 8-week period in the group receiving active treprostinil. Adverse events including headache, diarrhea, flushing, jaw pain, and foot pain were common in the treprostinil group, as they are with epoprostenol. An unexpected adverse effect was pain, which was occasionally severe and often associated with erythema and induration, at the site of the subcutaneous infusion. This occurred in nearly all the patients receiving active therapy. This proof-of-concept trial[19] demonstrated that this novel subcutaneous agent could be administered safely and effectively on an outpatient basis, and paved the way for the larger pivotal trial.

The largest placebo-controlled randomized study for PAH was an international trial[20] assessing the efficacy of subcutaneously delivered treprostinil in patients with PAH, either IPAH or PAH associated with connective tissue disease or congenital systemic to pulmonary shunts. Patients were enrolled between November 1998 and October 1999 in 24 centers in North America and 16 centers in Europe, Australia, and Israel. Four hundred seventy patients were randomly assigned to receive either continuous subcutaneous infusion of treprostinil plus conven-

tional therapy or continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. Because of the infusion site pain and reaction that occurred in the proof-of-concept trial,[19] the dosing strategy called for lower doses at initiation with a maximal allowable dose at the end of 12 weeks of 22.5 ng/kg/min. The primary end point of this trial was exercise capacity as measured by the 6-min walk distance, which improved in the treprostinil group and was unchanged with placebo. The median between treatment group difference was 16 m (p = 0.006). This effect on exercise tolerance appeared to be dose related. The patients in the lowest two quartiles of dosing experienced little improvement in 6-min walk distance, while patients in the highest quartile of dosing (> 13.8 ng/kg/min) demonstrated an improvement of 36 m in 6-min walk distance. Other indices of well-being, including the dyspnea fatigue rating and the Borg dyspnea scale, confirmed an improvement with treprostinil therapy. Treprostinil also demonstrated a significant improvement in the hemodynamic parameters of mean right atrial pressure, mPAP, cardiac index, PVR, and mixed venous oxygen saturation. Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common. Eighty-five percent of patients complained of infusion site pain, and 83% had erythema or induration at the infusion site.

Although statistically significant, the 16-m improvement in 6-min walk distance was relatively modest, and less than the improvements demonstrated in the trials,[11,12] with IV epoprostenol for both IPAH and PAH related to the scleroderma spectrum of disease, which demonstrated treatment effects of 47 m and 99 m, respectively. The reasons for this are multifactorial. The entry criteria for the treprostinil trial were much broader than for either of the epoprostenol trials. The epoprostenol trials included only patients who were functional class III and IV. Fifty-three functional class II patients were enrolled into the treprostinil trial. Their treatment effect in the 6-min walk distance was only 2 m, compared to 17 m for the 382 patients who were functional class III and 54 m for the 34 patients who were functional class IV. The baseline 6-min walk distance in the treprostinil study was 326 ± 5 m ($\pm$ SE) in the active treprostinil group and 327 ± 6 m in the placebo group; in comparison, the baseline 6-min walk distance in the IPAH epoprostenol trial was 315 m in the epoprostenol-plus-conventional therapy group vs 270 m in the conventional therapy alone group.[11] In the scleroderma epoprostenol trial,[12] the baseline 6-min walk distance was 272 m in the epoprostenol-plus-conventional therapy group and 240 m in the conventional therapy alone group.

This suggests that the patient population was less ill in the treprostinil trial,[20] and this may have contributed to the less impressive treatment effect. The treatment effect was also related to the baseline walk in the treprostinil trial. Patients who were able to walk between 351 m and 450 m did not demonstrate a treatment effect at all, whereas those patients who were able to walk in the lowest category of 50 to 150 m demonstrated a treatment effect of 51 m. The treprostinil trial included a broader range of patients with PAH. In addition to the inclusion of patients with IPAH and PAH associated with the scleroderma spectrum of diseases, PAH associated with congenital heart disease was included. This group had been untested in the past, and in the treprostinil study did not demonstrate any treatment effect at all. This may, in part, be related to their long-standing disease and the difficulty of making an impact on such a process over a short 12-week period.

The nemesis of subcutaneous treprostinil has been pain and erythema at the infusion site. A variety of therapies have been attempted to control this adverse effect, although none have emerged as uniformly successful. Local remedies such as topical hot and cold packs and topical analgesics and anti-inflammatory agents have been variably effective. Some patients respond to oral analgesics such as nonsteroidal anti-inflammatory drugs. Site pain and erythema sometimes improve after several months of therapy. Some patients find that moving the infusion site every 3 days as opposed to every day is useful. The infusion site most commonly used is the subcutaneous abdominal fat, although some patients were able to use the outer hips and thighs and underside of the upper arm. Because of the longer half-life of treprostinil, interruptions of the drug due to dislodgment of the catheter or pump malfunction tend to be less serious. In such instances, the catheter can be replaced or the pump switched with the individual's backup pump without any serious consequences. The Mini-Med pump (Medtronic Mini-Med, Northridge, CA) used to administer treprostinil is smaller than the CADD pump (Smith's Medical MD, St. Paul, MN) used to administer epoprostenol, and is approximately the size of a pager. The drug comes in a premixed and prefilled syringe, and therefore the patient needs only to place the syringe in the pump and does not have to mix the medication in a sterile fashion on a daily basis.

Inhaled Iloprost

Iloprost is a chemically stable prostacyclin analog available for IV, oral, and aerosol administration. It has a serum half-life of 20 to 25 min.[21] Inhaled therapy for PAH is an attractive concept that has been applied to clinical practice, > 10 years ago, with the use of inhaled NO.[22] Since intra-acinar pulmonary arteries are closely surrounded by alveolar units, it is possible to vasodilate these vessels by an alveolar deposition of vasodilators. It is critical that aerosolized particles be small enough (diameter, 3 to 5 pm) to ensure alveolar deposition.[23]

In IPAH, acute inhalation of iloprost resulted in a more potent pulmonary vasodilator effect than acute NO inhalation.[24] For long-term use, the relatively short duration of action of inhaled iloprost requires six to nine inhalations a day to obtain a sustained clinical benefit. With jet nebulizers, the duration of each inhalation takes approximately 15 min[23]; with alternative devices such as ultrasound nebulizers, the inhalation time can be reduced to approximately 5 min.[23]

In a 3-month, open, uncontrolled study[25] of 19 patients with various forms of PAH, inhaled iloprost at a daily dose of 50 to 200 μg in 6 to 12 inhalations a day improved functional class, exercise capacity (mean increase of the 6-min walking distance of 148 m), and pulmonary hemodynamics. Four patients died during the 3-month study period.

In a 1-year, open, uncontrolled study[26] of 24 patients with IPAH, aerosolized iloprost at a daily dose of 100 to 150 μg in six to eight inhalations per day improved exercise capacity (mean increase of the 6-min walking distance of 75 m) and pulmonary hemodynamics. The treatment was generally well tolerated except for mild coughing, minor headache, and jaw pain in some patients.

A 3-month, randomized, double-blind, placebo-controlled European multicenter trial[27] with inhaled iloprost was performed. A total of 203 NYHA functional class III and IV patients with IPAH, and PAH occurring in association with collagen vascular disease or inoperable chronic thromboembolic PAH, were enrolled. The daily dose of iloprost was 2.5 μg or 5 μg six times or nine times a day (maximum dose, 45 μg/d; median dose, 30 μg/d). The primary combined end point of a 10% improvement in the 6-min walking distance and NYHA functional class improvement in the absence of clinical deterioration or death was achieved in 17% of treated patients, compared to 5% in patients receiving placebo (p = 0.007). The treatment effect on the 6-min walking 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. There was also a statistically significant beneficial effect of iloprost on NYHA functional class (p < 0.05), quality of life (p < 0.05), and the Mahler dyspnea index (p < 0.05). As compared with baseline values, hemodynamic variables were significantly improved at 3 months when measured after

iloprost inhalation. Importantly, these hemodynamic variables were largely unchanged when measured before inhalation, and were significantly worse in the placebo group. One patient died during the study period in the iloprost group vs four patients in the placebo group (not significant). Overall, inhaled iloprost was well tolerated; cough, flushing, and headache occurred more frequently in the iloprost group. These adverse events were mild and mostly transient. Syncope occurred with similar frequency in the two groups, but was more frequently considered to be serious in the iloprost group, although this adverse effect was not associated with clinical deterioration.

In conclusion, based on available data, it appears as though inhaled iloprost is a safe, effective, and well-tolerated treatment for severe PAH. It is currently approved in Europe for IPAH in patients in NYHA functional class III. The most important drawback of inhaled iloprost is related to the relatively short duration of action, requiring the use of six to nine inhalations a day, which is not convenient for patients. In addition, the hemodynamic effects of inhaled iloprost disappear within 30 to 90 min after inhalation.

Beraprost

Beraprost sodium is the first chemically stable and orally active prostacyclin analog.[28] It is absorbed rapidly in fasting conditions; peak concentration is reached after 30 min and elimination half-life is 35 to 40 min after oral administration.[29] In a monocrotaline-induced PH model, beraprost sodium has been shown to have a protective effect on the development of PH lesions.[30] In addition, high doses of beraprost appear to have inotropic and chronotropic effects in the isolated guinea pig myocardium.[31] Beraprost has also been evaluated in peripheral vascular disorders such as intermittent claudication,[32] Raynaud phenomenon, and digital necrosis in systemic sclerosis,[33] with variable results.

Since 1995, beraprost has been used to treat PAH in Japan. Several small, open, uncontrolled studies[28,34] have reported beneficial hemodynamic effects with beraprost in patients with IPAH. In a retrospective, open uncontrolled study, Nagaya et al[35] reported improved survival in 24 patients with IPAH treated with beraprost, compared to a similar group of 34 patients receiving conventional therapy. In this study,[35] the 3-year survival rate was 76% in the beraprost group, compared with 44% in the conventional therapy group.

To date, two randomized, double-blind, placebo-controlled trials[36,37] studied beraprost in PAH. The first study[36] was a 12-week, double blind, random-

ized, placebo-controlled trial performed in 130 patients in NYHA functional class II and III with PAH of various etiologies (IPAH, PAH associated with connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension, or HIV infection). Beraprost (median dose, 80 μg po qd) increased exercise capacity as assessed by the 6-min walking distance. The treatment effect was 25 m in the overall population; however, the treatment effect was 45 m in the patients with IPAH, whereas there were no significant changes in the exercise capacity of subjects with PAH and associated conditions. There were no significant changes in cardiopulmonary hemodynamics, and no difference in survival was detected between the two treatment groups. Side effects linked to systemic vasodilatation were frequent, mainly in the initial titration period, suggesting that tolerance may affect the long-term results with beraprost in the treatment of PAH. A second trial[37] evaluated the effects of beraprost therapy for PAH in 116 patients in NYHA functional class II and III: a 12-month, double-blind, randomized, placebo-controlled study. This study[37] showed that the beraprost-treated patients had less disease progression at 6 months and confirmed the results of the previous trial[36]: improved 6-min walk distance at 3 months (+ 22 m from baseline) and 6 months (+ 31 m from baseline), as compared to placebo; however, this improvement was no longer present at 9 months or 12 months. There were no significant changes in hemodynamics at month 12 vs baseline. The survival rate was similar for both treatment groups. These data raise the possibility that the beneficial effects of beraprost may attenuate with time.

Beraprost is an approved therapy for PAH in Japan, and is currently under evaluation by the European Agency for the Evaluation of Medicinal Product. Whether beraprost will prove efficacious as a concomitant medical therapy in combination/multimodal treatment regimens requires further study. In addition, the development of an extended-release form should improve the overall risk-benefit profile for treating PAH patients with beraprost.

Specific recommendations regarding the use of prostanoids in the treatment of PAH follow the section immediately below on "Endothelin Antagonists." This facilitates the use of an approach based on disease and functional severity, which is more applicable to clinical practice and is summarized in the treatment algorithm (Fig 1).

Endothelin Antagonists

Introduction/Rationale

Endothelin-receptor antagonism is a promising therapeutic approach supported by increasing evi-
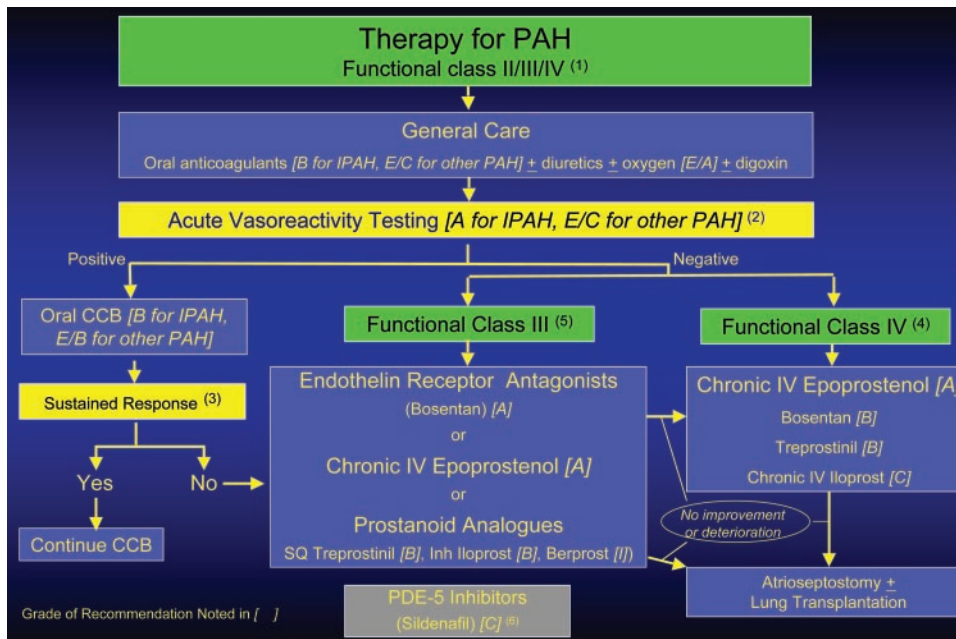
FIGURE 1. This algorithm is based on one developed at the third World Symposium on Pulmonary Arterial Hypertension, held in Venice, Italy, June 23 to 25, 2003. It has been modified slightly, and the grading of recommendations, based on the system used in this document, is noted in the algorithm in the italicized brackets. *1*: The algorithm is focused on patients in functional class III or IV. Patients in functional class II who are not candidates for, or who have failed, CCB therapy may benefit from treatment. However, limited data are available, and no specific drug can be recommended. Therapies in the algorithm have been evaluated mainly in IPAH, and in PAH associated with scleroderma or due to anorexigens. Extrapolation of these recommendations to the other PAH subgroups should be done with caution. *2*: A positive acute response to vasodilators is defined as a fall in mPAP of at least 10 mm Hg to $\leq$ 40 mm Hg, with an increased or unchanged CO during acute challenge with inhaled NO, IV epoprostenol, or IV adenosine. *3*: Sustained response to CCBs is defined as patients being in functional class I or II with near-normal hemodynamics after several months of treatment. *4*: Most experts recommend that patients in functional class IV in unstable condition be treated with IV epoprostenol. *5*: In patients in functional class III, first-line therapy may include oral endothelin-receptor antagonists, long-term IV epoprostenol, or prostanoid analogues. *6*: Early reports show promising results regarding the potential therapeutic efficacy of sildenafil in the management of patients with chronic PAH. Despite these promising reports, appropriately designed randomized clinical trials are needed (currently in progress). In patients with PAH who have failed or are not candidates for other available therapy, treatment with sildenafil may be considered. SQ = subcutaneous; Inh = inhaled; PDE = phosphodiesterase.

dence of the pathogenic role of endothelin-1 in PAH.[38] Endothelin-1 is a potent vasoconstrictor and a smooth-muscle mitogen that might contribute to the increase in vascular tone and the pulmonary vascular hypertrophy associated with PAH.[39] In addition, endothelin-1 expression, production, and concentration in plasma[40,41] and lung tissue[42] are elevated in patients with PAH, and these levels are correlated with disease severity.[42] In a small cohort of patients with IPAH, plasma concentrations of endothelin correlated with PAP and PVR, as well as with exercise capacity.[43]

Two distinct endothelin-receptor isoforms have been identified, ET_A and ET_B.[44] Activation of ET_A receptors facilitates vasoconstriction and proliferation of vascular smooth-muscle cells.[44] In contrast, ET_B receptors are thought to be principally involved

in the clearance of endothelin, particularly in the vascular beds of the lung and kidney.[44] Activation of ET_B receptors may also cause vasodilation and NO release. There is considerable debate as to whether it is preferable to block both the ET_A and ET_B receptors, or to target the ET_A receptor alone. It is argued by some that selective antagonism of ET_A receptors may be beneficial for the treatment of PAH, due to maintenance of the vasodilator and clearance functions of ET_B receptors. In PH models,[39,45–47] bosentan, an orally active nonpeptide antagonist of both endothelin-receptor subtypes (ET_A and ET_B), prevents and even reverses the development of PH, pulmonary vascular remodeling, and right ventricular hypertrophy, independent of the triggering mechanisms. Sitaxsentan sodium, hereafter referred to as sitaxsentan, is a potent endothelin-receptor

antagonist that has oral bioavailability and a long duration of action.[48] Sitaxsentan is approximately 6,000-fold more selective as an antagonist for ET_A compared with ET_B receptors. Both bosentan and sitaxsentan have undergone randomized and controlled clinical trials in patients with PAH. The results of these studies will be summarized below.

Bosentan

The first randomized, double-blind, placebo-controlled, multicenter study[49] of bosentan was designed to assess the effects of bosentan on exercise capacity and cardiopulmonary hemodynamics, as well as to assess its safety and tolerability in patients with severe PAH. Patients eligible for this study had symptomatic, severe IPAH or PAH occurring in association with scleroderma (in functional classes III or IV, according to the 1998 modified NYHA classification), despite prior treatment, which included vasodilators, anticoagulants, diuretics, cardiac glycosides, or supplemental oxygen. No class IV patients were actually enrolled in the study. Patients were excluded if they had started or stopped any of the above treatments within 1 month of screening, or if they were receiving long-term treatment with epoprostenol. To avoid potential drug interactions, patients were excluded if they had received gliben-clamide (glyburide) or cyclosporine within 1 month of enrollment. A baseline 6-min walking distance between 150 m and 500 m, an mPAP > 25 mm Hg, a pulmonary capillary wedge pressure < 15 mm Hg, and a PVR > 240 dyne·s·cm^{-5} were required for inclusion. The study was conducted in five centers in the United States and one center in France. Thirty-two patients were randomized to receive bosentan or placebo (2:1 ratio). Patients received either bosentan 62.5 mg bid for the first 4 weeks, followed by the target dose (125 mg bid), unless drug-related adverse events were observed (*eg*, hypotension), or matching doses of placebo. Treatment groups were well matched with respect to baseline characteristics. After 12 weeks of treatment with bosentan, the distance walked in 6 min improved by 70 m (from 360 ± 19 m at baseline to 430 ± 14 m at week 12; $p < 0.05$) [$\pm$ SEM], whereas no improvement was seen with placebo (355 ± 25 m at baseline and 349 ± 44 m at week 12). The median change from baseline was 51 m with bosentan and – 6 m with placebo. The difference between treatment groups in the mean change in the 6-min walking distance was 76 ± 31 m in favor of bosentan (95% CI, 12 to 139 m; $p = 0.021$). Treatment with bosentan significantly improved cardiopulmonary hemodynamics from baseline to week 12 compared with placebo. Bosentan improved cardiac index; the difference

between treatment groups in the mean change at week 12 was 1.0 ± 0.2 L/min/m^2 (mean $\pm$ SEM) in favor of bosentan (95% CI, 0.6 to 1.4 L/min/m^2; $p < 0.001$). PVR was significantly decreased with bosentan, whereas it was increased with placebo (95% CI, – 608 to – 221 dyne·s·cm^{-5}; $p < 0.001$). Treatment with bosentan decreased the mPAP, the pulmonary capillary wedge pressure, and the mean right atrial pressure. In contrast, all three variables increased in the placebo group. Functional class also improved in patients treated with bosentan. No patient received a lung transplant or died during the study. During the first 12 weeks of treatment, adverse events were transient and similar in frequency and nature in the two groups (7 of 11 patients [63.6%] in the placebo group, and 9 of 21 patients [42.9%] in the bosentan group). Asymptomatic increases in hepatic aminotransferases were observed in two bosentan-treated patients, but these normalized without discontinuation or change of dose.

In a second double-blind, placebo-controlled study, bosentan was evaluated in 213 patients with PAH (either primary or associated with connective tissue disease) who were equally randomized to placebo, bosentan 125 bid, or bosentan 250 mg bid for a minimum of 16 weeks (62.5 mg bid for 4 weeks, then target dose).[50] The primary end point was the change in exercise capacity as assessed by the 6-min walk. Secondary end points included changes in Borg dyspnea index, World Health Organization functional class, and time from randomization to clinical worsening. Enrolled patients had symptomatic, severe PAH (World Health Organization functional classes III to IV)[51] despite treatment with anticoagulants, and/or vasodilators, diuretics, cardiac glycosides, or supplemental oxygen. Inclusion and exclusion criteria were similar to those in the first study of bosentan, described above. The study was conducted in 27 centers in Europe, North America, Israel, and Australia. Two hundred thirteen patients were equally randomized to receive either bosentan (62.5 mg bid for 4 weeks), followed by the target dose (125 mg bid or 250 mg bid) or matching doses of placebo (144 patients received bosentan and 69 patients received placebo). The placebo and bosentan groups were well matched with respect to demographics and baseline characteristics. After 16 weeks of treatment, bosentan improved the distance walked in 6 min by 36 m, whereas deterioration (– 8 m) was seen with placebo. The difference between treatment groups in the mean change in the 6-min walking distance was 44 m in favor of bosentan (95% CI, 21 to 67 m; $p = 0.0002$). Although both bosentan dosages induced a significant treatment effect, the improvement was more pronounced for the 250 mg bid dosage than for the 125 mg bid dosage (+ 54 m

and $+35$ m, respectively). However, no dose response for efficacy could be ascertained; the observed difference in the walking distance at week 16 for the two dose groups ($\Delta = 20$ m) was not statistically significant and was already present at week 4 ($\Delta = 12$ m) when all patients were treated with 62.5 mg bid. The risk of clinical worsening was significantly reduced by bosentan compared to placebo ($p = 0.0015$, with log-rank test). The most frequent adverse event in both treatment groups was headache (21% in the bosentan group and 19% in the placebo group). Adverse events that were more frequent in the placebo group than in the bosentan group were disease related, and included dizziness, aggravated PAH, cough, and dyspnea. Conversely, abnormal hepatic function (as indicated by elevated levels of alanine aminotransferase and/or aspartate aminotransferase), syncope, and flushing occurred more frequently in the bosentan group. Study medication had to be prematurely discontinued in nine patients (6%) in the bosentan group and five patients (7%) in the placebo group. The most frequent cause for withdrawal was abnormal hepatic function in the bosentan group (2% for bosentan vs 0% for placebo), and aggravated PAH and syncope in the placebo group (respectively, 6% and 3% for placebo vs 1.4% and 0% for bosentan). Abnormal hepatic function was found to be dose dependent. It was more frequently reported as an adverse event in the high-dosage bosentan group (250 mg bid) than in the low-dosage group (125 mg bid) [14% vs 5%, respectively]. Increases in hepatic enzymes more than three times the upper limit of normal occurred in 10 patients (14%) in each bosentan-dosage group; two patients (2.7%) in the 125 mg bid group and five patients (7.1%) in the 250 mg bid group experienced elevations more than eight times the upper limit of normal. Hepatic function abnormalities were transient except for three patients (all in the high-dosage bosentan group); these patients had to be withdrawn prematurely from the study. Three patients died during the course of the study: two placebo patients died of aggravated PAH, and one bosentan patient (125 mg bid) died of cardiac failure.

There are several notable potential toxicities associated with the use of bosentan. Due to the risk of potential hepatic toxicity discussed above, the US FDA requires that liver function tests be performed at least monthly in patients receiving this drug. Bosentan use may also be associated with the development of anemia, which seems typically to be mild. The hemoglobin/hematocrit should be checked regularly. Due to the potential teratogenic effects of bosentan, careful attention must be paid to the use of adequate contraception in women of childbearing age. It is important to note that bosentan may decrease the efficacy of hormonal contraceptive techniques, and for this reason they should not be used alone. Rather, it is suggested that some other form of contraception be included, such as the use of double-barrier techniques (condom and diaphragm) with a spermicide. Regular pregnancy testing is recommended in women of childbearing age. There is concern that the endothelin antagonists as a class may be capable of causing testicular atrophy and male infertility. Younger men who may consider conceiving should be counseled regarding this possibility prior to taking these drugs.

Sitaxsentan

In the first randomized, double-blind, placebo-controlled trial with sitaxsentan in PAH,[51a] 178 NYHA class II, III and IV patients with either IPAH, PAH related to connective tissue disease, or PAH related to congenital systemic to pulmonary shunts were equally randomized to receive placebo, sitaxsentan 100 mg po qd, or sitaxsentan 300 mg po qd. Sitaxsentan improved exercise capacity (6-min walk distance) and functional class after 12 weeks of treatment. These functional benefits occurred with both the 100-mg and the 300-mg doses. 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 improved in 16 of 55 patients (29%) in the 100-mg group, and in 19 of 63 patients (30%) in the 300-mg group. In contrast, only 9 of 60 patients (15%) in the placebo group had improvement in NYHA functional class. PVR significantly decreased with sitaxsentan treatment from baseline to week 12 (mean $\pm$ SD for 100-mg group, $1,025 \pm 694$ to 805 ± 553 dyne·s·cm^{-5} [$p < 0.001$]; and 300-mg group, 946 ± 484 to 753 ± 524 dyne·s·cm^{-5} [$p < 0.001$], and increased with placebo (911 ± 484 to 960 ± 535 dyne·s·cm^{-5}). Cardiac index did not change in the placebo group after 12 weeks of treatment (2.4 ± 0.8 to 2.4 ± 0.9 L/min/m^2), but increased significantly with sitaxsentan treatment (100 mg, 2.4 ± 0.8 to 2.7 ± 0.8 L/min/m^2 [$p < 0.02$]; 300 mg, 2.3 ± 0.7 to 2.7 ± 0.9 L/min/m^2 [$p < 0.001$]. Similar improvements in 6-min walk, functional class, and hemodynamics with both doses suggest that significant saturation of ET_A receptors occurred with the 100-mg and 300-mg doses, which were at or near the top of the dose-response curve for efficacy. In contrast, the incidence of liver function abnormalities was more favorable for the 100-mg dose, *ie*, the incidence of elevated aminotransferase values (more than three times normal), which reversed in all cases, was 3% for the placebo group, 0% for the 100-mg group, and 10% for the 300-mg group. It should be noted that in an earlier

pilot study,[52] sitaxsentan was associated with fatal hepatitis when used at higher doses. In the larger randomized trial,[51a] the most frequently reported clinical adverse events with sitaxsentan treatment (and more frequent than in placebo) were headache, peripheral edema, nausea, nasal congestion, and dizziness, reactions previously noted with endothelin-receptor antagonists. The most frequently reported laboratory adverse event was increased INR 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. Observations during the trial showed that this interaction can be managed by reducing the warfarin dose to achieve the desired INR. A second randomized, double-blind, placebo-controlled multicenter study is in progress.

Ambrisentan

A third endothelin antagonist, ambrisentan, is currently in phase III clinical trials in patients with PAH. This ET_A-selective antagonist is slightly different biochemically. Information on relative safety and efficacy will hopefully be forthcoming in the near future.

Recommendations

10. **Patients with PAH in functional class II who are not candidates for, or who have failed, CCB therapy may benefit from treatment. However, limited data are available, and no specific drug can be recommended. Enrollment in clinical trials is encouraged.** Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/B.

11. **Patients with PAH 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)**. Level of evidence: good; benefit: substantial; grade of recommendation: A.
    b. **IV epoprostenol**. Level of evidence: good; benefit: substantial; grade of recommendation: A.
    c. **Subcutaneous treprostinil.** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.
    d. **Inhaled iloprost.** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.
    e. **Beraprost.** Level of evidence: good; benefit: conflicting; grade of recommendation: I.

12. **Patients with PAH 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 patients with PAH in functional class IV include, in no hierarchical order:**
    a. **Endothelin-receptor antagonists (bosentan)**. Level of evidence: fair; benefit: intermediate; grade of recommendation: B.
    b. **Subcutaneous treprostinil.** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.
    c. **Inhaled iloprost.** Level of evidence: low; benefit: small; grade of recommendation: C.

Phosphodiesterase Inhibitors

Rationale

Mechanisms that modulate cyclic guanosine 3′-5′ monophosphate (cGMP) content in vascular smooth muscle play critical roles in the regulation of vascular tone, growth, and structure. The vasodilator effects of NO are dependent on its ability to augment and sustain cGMP content in vascular smooth muscle. Once produced, NO directly activates soluble guanylate cyclase, which increases cGMP production. cGMP then activates cGMP kinase, opens potassium channels, and causes vasorelaxation. The effects of intracellular cGMP are short lived, however, due to the rapid degradation of cGMP by phosphodiesterases.[53,54] Phosphodiesterases are a family of enzymes that hydrolyze the cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cGMP, and limit their intracellular signaling properties by generating inactive products (5′-adenosine monophosphate and 5′-guanosine monophosphate, respectively). Whereas inhibition of cAMP-specific phosphodiesterases (type 3) has played a major role in the treatment of asthma (*eg*, theophylline) and myocardial dysfunction (*eg*, milronone and amrinone), drugs that specifically inhibit cAMP-specific phosphodiesterases have relatively weak effects on the pulmonary circulation. In striking contrast, however, drugs that selectively inhibit cGMP-specific phosphodiesterases (phosphodiesterase type 5 inhibitors) augment the pulmonary vascular response to endogenous or inhaled NO in models of PH.[55–61] Phosphodiesterase type 5 is strongly expressed in the lung, and phosphodiesterase type 5 gene expression and activity are increased in chronic PH.[62,63] Several phosphodiesterase type 5 inhibitors, including dipyridamole, E4021, zaprinast, DMPPO, and others, cause potent pulmonary vasodilation in animal models[55–59,61] of acute and chronic PH.

Dipyridamole

Early clinical studies[60,64] demonstrated that dipyridamole can lower PVR, attenuate hypoxic pulmonary vasoconstriction, decrease PH and, at least in some cases, augment or prolong the effects of inhaled NO in children with PH. Some patients who failed to respond to inhaled NO responded to the combination of inhaled NO plus dipyridamole.[60] These findings suggest that phosphodiesterase type 5 inhibition may be an effective clinical strategy for the treatment of PAH, but have been limited by the lack of potency and selectivity, and potential systemic effects of dipyridamole.

Sildenafil

Sildenafil is a potent and highly specific phosphodiesterase type 5 inhibitor, which has been proven as a safe and effective therapy for erectile dysfunction. Based on growing understanding of phosphodiesterase type 5 activity in the pulmonary circulation, uncontrolled clinical studies have examined the acute hemodynamic effects of sildenafil and its potential role in the long-term treatment of patients with PAH. Reports have shown that sildenafil blocks acute hypoxic pulmonary vasoconstriction in healthy adult volunteers,[65] and acutely reduces mPAP in patients with PAH.[66] Michelakis et al[66] studied the effects of sildenafil in 13 patients with PAH, and reported a reduction in mPAP and PVR, with an increase in cardiac index. In comparison with inhaled NO, sildenafil had similar effects on the reduction in mPAP; unlike NO, sildenafil also had apparent systemic hemodynamic effects.[66,67]

When combined with inhaled NO, sildenafil appears to augment and prolong the effects of inhaled NO.[66,67] Sildenafil with inhaled NO reduced pulmonary artery wedge pressure and augmented cardiac index, and achieved a greater decrease in PVR than with either agent alone. As observed with dipyridamole, sildenafil treatment appears to prevent rebound pulmonary vasoconstriction after acute withdrawal of inhaled NO.[68]

In addition to acute vasoreactivity studies of sildenafil combined with inhaled NO, the separate and combined effects of sildenafil and iloprost in patients with PAH have also been reported.[69,70] Aerosolized iloprost caused a more marked fall in mPAP and PVR than sildenafil, but combined treatment achieved a greater and more prolonged decrease in mPAP and PVR than either agent alone.[69]

Several reports of nonrandomized, single-center studies of patients with PAH treated with long-term sildenafil suggest promise for sildenafil as a therapeutic agent.[70–72] Bharani and associates[71] treated 10 patients with sildenafil or placebo for 2 weeks, using a cross-over design. After 2 weeks of sildenafil treatment, patients had significantly improved their 6-min walk test and dyspnea index, with decreased echocardiographic estimates of systolic PAP. In another study,[72] 29 patients were treated with sildenafil (25 to 100 mg tid) for 5 to 20 months. These authors reported improvements in NYHA functional class, 6-min walk test, and dyspnea index, as well as modest decreases in noninvasive assessments of systolic PAP.

Many patients with severe chronic thromboembolic PH (CTEPH) have progressive PH, despite long-term medical and surgical therapies, including anticoagulation. In some patients with CTEPH, vascular remodeling and enhanced reactivity can progress in nonoccluded vessels, thus supporting the premise that long-term sildenafil therapy may be effective in CTEPH. Gohfrani et al[73] studied the effects of long-term sildenafil treatment of patients with CTEPH for 6 months. They found that sildenafil reduced mPAP and PVR by 15% and 30%, respectively; increased cardiac index by 17%; and increased 6-min walking distance. There were no signs of significant side effects, other than headache and nausea, suggesting that long-term sildenafil therapy may be effective in the long-term management of severe PAH in patients with CTEPH.

Little is known about the potential role of sildenafil in long-term combination therapy. Stiebellehner et al[74] treated three patients with PAH who were doing poorly despite long-term IV epoprostenol therapy, and reported substantial clinical improvement with the addition of sildenafil. These findings suggest the potential therapeutic strategy of combined agents for long-term management of severe PAH. Although prostacyclin primarily acts via stimulation of cAMP, it is interesting that phosphodiesterase type 5 inhibition augments the vasodilator and chronic effects of prostacyclin. Mechanisms underlying the augmented response with sildenafil and prostanoids are incompletely understood, but these findings suggest significant cross-talk between the cyclic nucleotides. For example, cGMP inhibits phosphodiesterase type 3 activity, which could augment smooth muscle cAMP content. Alternatively, these may simply reflect additive effects of parallel pathways, or prostacyclin may act in part by stimulation of the NO-cGMP signaling.

Thus, early reports show promising results regarding the potential therapeutic efficacy of sildenafil in the long-term management of patients with chronic PAH. These studies suggest efficacy with relatively few minor side effects (eg, headache, nasal congestion, and visual disturbances). Sildenafil treatment in animal models[75,76] with experimental lung injury have also shown reduction in PAP, although gas exchange worsened due to impaired ventilation-

perfusion matching. These findings suggest a need for caution in the treatment of PH in patients with severe lung disease. The potential utility of sildenafil has particular appeal as a long-term treatment due to its ease of oral administration. Despite promising reports, appropriately designed, RCTs are needed (currently in progress). Additional studies are also needed to compare the efficacy of sildenafil with other therapies, as well as its role in combination therapy.

Recommendations

14. In patients with PAH who have failed or are not candidates for other available therapy, treatment with sildenafil should be considered. Level of evidence: low; benefit: intermediate; grade of recommendation: C.

NO AND ARGININE

Rationale

NO contributes to the maintenance of normal vascular function and structure. Recognition of the importance of NO as an endogenous vasodilator[77] was followed by experimental and clinical observations indicating its physiologic roles in the maintenance of normal basal vascular resistance.[77–79] That deficient function of the NO signaling system may be an important contributor to the pathogenesis of diverse cardiovascular disorders has come from abundant observations of impaired endothelium-mediated vasodilator function in patients and experimental animals with hypercholesterolemia,[80–83] coronary artery disease,[84–91] congestive heart failure,[92–95] diabetes,[96] peripheral vascular disease,[97] systemic hypertension,[87,98,99] and aging.[87,100–102] NO is particularly important in the normal adaptation of the lung circulation at birth, and impaired NO production may contribute to the development of neonatal PH.[103,104] NO continues to modulate pulmonary vascular tone and structure during adult life, as illustrated by the marked susceptibility for PH in mice with genetic impairment of NO production.[105] In addition to its action as a vasodilator, several studies[106,107] suggest that NO exerts important effects on vascular structure, which include maintenance of a thin vascular wall and large lumen in experimental atherogenesis and increased flow states. NO has also been shown to have antiplatelet activity,[108–110] anti-inflammatory and anti-oxidant properties, modulatory effects on angiogenesis, and can alter the expression and activity of several vascular growth factors and vasoactive products.

NO is generated by three isoforms of NO synthase (NOS), which are present in multiple and diverse cell types and continuously active (constitutive; types I and III) in endothelium, or "inducible" (type II) in other cells, such as macrophages, bronchial epithelium, and vascular smooth muscle. Regulation of NOS is complex, and includes growth factors (such as vascular endothelial growth factor), hormones (including estradiol), oxygen tension, hemodynamics, and other factors. In addition, it is clear that the amino acid, L-arginine, is the sole substrate for NOS and thus is essential for NO production. It is estimated that the average diet is borderline in arginine content,[111,112] and circulating levels can be reduced by administration of arginine-deficient protein,[111,112] by pregnancy,[113–117] aging,[118] or stress.[118] Still, *in vivo* arginine levels have been thought to be more than sufficient for NO synthesis because at usual plasma levels of 50 to 100 μmol/L, active transport produces intracellular levels of 1,000 μmol/L, which vastly exceed the Km for NOS of 1 to 3 μmol/L.[119] However, exogenous arginine seems to increase NO production. Arginine reaches the interior of the cell by active transport,[120] and defects in transport mechanisms might contribute to arginine dependence by raising the extracellular levels needed to provide adequate delivery. In endothelium, the arginine transporter is tightly colocalized with NOS.[121] If this linkage were disrupted by endothelial injury; normal extracellular levels might become insufficient for NO generation. Arginine deficiency has been shown to accompany persistent PH of the newborn (PPHN),[122] and acute L-arginine infusion (500 mg/kg over 30 min) in infants with PPHN resulted in a rise in PaO_2 over the 5-h period following infusion.[123] Whether long-term arginine supplementation can reduce ongoing vascular injury and lead to structural improvement in the lung circulation in patients with PAH is unknown. Such a possibility would be supported by the finding that chronic administration of L-arginine ameliorates chronic PH and vascular remodeling induced in rats by either chronic hypoxia or monocrotaline injection.[124]

Inhaled NO

After the recognition that endogenous NO production accounts for the "endothelium-derived relaxing factor" activity in the vessel wall,[125] inhaled NO was subsequently shown to have selective and potent pulmonary vasodilator effects during brief treatment of adults with IPAH.[22] Subsequent studies demonstrated that inhaled NO is a potent pulmonary vasodilator in multiple settings, including newborns with PH (PPHN), children with congenital heart disease, postoperative PH, ARDS, lung transplantation, and others.[126] It has been shown to be of

substantial benefit in PPHN, decreasing the need for support with extracorporeal membrane oxygenation.[127,128] Although inhaled NO has been used extensively in diverse clinical settings, especially in intensive care medicine, FDA approval for this therapy is exclusively for newborns with hypoxemic respiratory failure at this time.

For patients with chronic PAH, the use of inhaled NO has been primarily for acute testing of pulmonary vasoreactivity during cardiac catheterization (see above), or for acute stabilization of patients during deterioration. Pulsed delivery of inhaled NO has been shown to effectively lower PVR in some patients,[129] and experience with the use of long-term inhaled NO therapy in children and adults with PAH has been described.[130] However, current experience with inhaled NO therapy for PAH has been extremely limited, and is reported only as isolated case reports. Although a small number of adult patients with PAH have received long-term inhaled NO, some with apparent benefit, long-term delivery of inhaled NO to adults with PAH has not been formally studied. Extensive work is needed to determine whether long-term inhaled NO in the ambulatory setting is safe, acceptable, feasible, and effective.

Arginine Supplementation

Efforts to acutely improve pulmonary hemodynamics in adults with pulmonary vascular disease by augmenting endogenous NO production with substrate (arginine) supplementation have been met with mixed results. Short-term administration of L-arginine (500 mg/kg infused over 30 min) in 10 subjects with PAH resulted in a reduction in mPAP by $15.8 \pm 3.6\%$ ($p < 0.005$) and PVR by $27 \pm 5.8\%$ ($p < 0.005$), compared with decreases of $13.0 \pm 5.5\%$ ($p < 0.005$) and $46.6 \pm 6.2\%$ ($p < 0.005$), respectively, for prostacyclin titrated to maximally tolerated doses ($\pm$ SEM).[131] The infusion of L-arginine resulted in markedly increased plasma levels of L-arginine, as well as a rise in plasma L-citrulline, and the peak plasma level of L-citrulline correlated significantly with the reductions in mPAP, possibly consistent with vasodilation mediated by NOS metabolism of exogenous L-arginine and increased NO production. A possible criticism of this study,[131] and the above-mentioned study in infants,[123] is the relatively high dose utilized (as indicated in the latter study by the marked increase in the plasma level of L-arginine). In contrast, a small study[132] of acute L-arginine infusion (12.63 g of L-arginine hydrochloride in 300 mL of 0.9% NaCl over 90 min) in four patients with IPAH demonstrated little favorable effect on pulmonary hemodynamics, and significant decreases in systemic resistance in two patients. Another short-term study[133] of L-

arginine infusion (500 mg/kg over 30 min) in five normotensive volunteers and five patients with systemic sclerosis and PAH demonstrated no significant effect on BP, heart rate, or skin temperature in the normotensive volunteers, nor on systemic or pulmonary hemodynamics in the systemic sclerotic group. cGMP levels did not significantly change in either group.

A study published by Nagaya et al[134] suggests that oral supplementation of L-arginine may have beneficial effects on hemodynamics and exercise capacity in patients with PAH. Acute hemodynamic responses to oral L-arginine (0.5 g/10 kg body weight) or placebo were examined in 19 patients with PAH. Cardiopulmonary exercise tests were performed to measure peak oxygen consumption and the ventilatory response to carbon dioxide production before and 1 week after treatment with L-arginine (1.5 g/10 kg body weight per day) or placebo. Oral supplementation of L-arginine significantly increased plasma L-citrulline, which indicated enhancement of NO production. Supplemental L-arginine produced a 9% decrease in mPAP (53 ± 4 to 48 ± 4 mm Hg, $p < 0.05$) and a 16% decrease in PVR (14.8 ± 1.5 to 12.4 ± 1.4 Wood units, $p < 0.05$). L-arginine modestly decreased mean systemic arterial pressure (92 ± 4 to 87 ± 3 mm Hg, $p < 0.05$) [$\pm$ SEM]. A 1-week supplementation of L-arginine resulted in a slight increase in peak oxygen uptake (831 ± 88 to 896 ± 92 mL/min, $p < 0.05$) and a significant decrease in the ventilatory response to carbon dioxide production (43 ± 4 to 37 ± 3, $p < 0.05$) without significant systemic hypotension. Hemodynamics and exercise capacity remained unchanged during placebo administration.

Unfortunately, despite growing use of oral arginine supplements, we are still lacking rigorous randomized single or multicenter trials of long-term oral arginine supplementation in patients with PAH. Potential drawbacks of arginine supplementation may include an increase in the concentration of polyamines, which are proproliferative. It is thus not clear at this time whether short-term effects will translate into long-term benefits. Further clinical studies are needed.

Combination Therapy

With the development of therapeutic agents with different mechanisms of action, considerable interest has developed in the possibility of combination therapy, similar to the strategies utilized in the treatment of systemic hypertension and many forms of cancer. Some agents, such as phosphodiesterase inhibitors, might enhance and prolong the effects of

others, like the prostanoids. Other combinations might simply approach the problem of PAH from different mechanistic angles, and therefore have at least partially additive effects. Such combinations not only offer the possibility of enhanced efficacy, but also may permit individual agents to be used in lower dosages, thereby minimizing toxicity. It is also possible that combination therapy could result in drug-drug interactions, with unexpected increases in toxicity. Unfortunately, the design of combination studies is complicated, as is obtaining funding from the pharmaceutical industry for their conduct.

The BREATHE-2 study was performed in patients beginning long-term IV therapy with epoprostenol. Such patients were randomized to also receive the oral dual-endothelin antagonist bosentan (see above) or placebo. Peer review and publication of this study is currently pending.

Special Situations

Children

In decades past, the early presentation of severe PAH during infancy or early childhood was typically associated with a rapidly progressive disease and fatal outcome. The National Institutes of Health PPH Registry in the 1980s initially suggested a worse survival in children < 16 years of age, with a mean survival of 10 months in contrast to adults, in whom the mean survival was 2.8 years after diagnosis.[135] However, this study[135] included only small numbers of pediatric cases, and preceded the availability of many of the currently available medical therapies. Over the past decade, several studies have highlighted successful clinical strategies in the management of children with severe PAH.[136] This may in part be related to the striking physiologic observation by Barst et al[137] and Sandoval et al,[138] which demonstrated that the acute pulmonary vascular response to vasodilators is more common in younger patients than adults (40% in children vs 20% in adults). These findings support the hypothesis that despite past reports of a higher mortality in children than adult patients if untreated, children with IPAH can do quite well with long-term vasodilator therapy. In fact, although data are limited, children with severe PAH who are treated with long-term epoprostenol infusions appear to have at least as good a response as seen with adults with IPAH.[137,139]

Overall, children with severe PAH are now treated with similar clinical strategies as applied in the management of adults with IPAH. However, few data have specifically examined clinical responses of children. For example, children with severe PH undergo a similar diagnostic evaluation as has been described in adults.[140] Typical studies include arterial blood gas and oxygen saturation measurements, a chest radiograph, pulmonary function and exercise testing, echocardiogram, ventilation-perfusion scan, chest CT, sleep studies, serologic studies for collagen vascular disease, liver enzyme tests, studies of hypercoagulability, HIV testing, and others.

As in adults with severe PAH, testing of pulmonary vasoreactivity during cardiac catheterization includes assessment of the acute response to a short-acting vasodilator, such as inhaled NO, IV epoprostenol, or IV adenosine, to determine if there is a role for long-term therapy with an oral CCB. In addition, the acute response to calcium-channel blockade is often studied during cardiac catheterization to assess therapeutic dose and the potential for adverse hemodynamic effects.

In general, although similar treatment strategies to those described in adults with IPAH are utilized in children, the doses per kilogram for many of the medications used (eg, CCBs, epoprostenol) are often significantly greater in children than in adults. The use of an anticoagulant such as warfarin is typically included in the treatment of children, although past clinical studies did not include children. Doses of warfarin are adjusted to maintain an INR between 1.5 and 2, except in younger, active infants, or in children who are hypercoagulable. CCB therapy is initiated in children with significant responsiveness to acute vasodilator testing during cardiac catheterization,[3] ie, ≥ 20% mPAP to ≤ 40 mm Hg with no change or an increase in CO. Sustained responsiveness to CCB therapy has been described, but data on long-term responses are lacking. Clinical indications for long-term IV epoprostenol therapy in children are similar to adults, but younger patients are often managed with higher doses than adults (eg, 50 to 80 ng/kg/min vs 20 to 40 ng/kg/min in adults). Anecdotally, the potential risks for line-related complications, including infections, breaks, and others, may be greater in younger children than adults. Specific data on the response to other prostanoids in children, such as oral beraprost, inhaled iloprost, or subcutaneous treprostinil, are currently lacking.

Recently, the pharmacokinetics, safety, and response to bosentan in pediatric patients with PAH have been reported[141]; this two-center, open-label study examined the acute and sustained (12 weeks) effects of bosentan in 18 patients between 3 years and 15 years of age with IPAH or PAH associated with congenital heart disease. As observed in adults, mPAP was reduced after 12 weeks of therapy, regardless of concurrent treatment with other pulmonary hypertensive medications. Side effects were rare, and the dosage regimens applied in this study appeared to be safe and effective.

Perhaps the most striking difference in medical therapy of severe PAH between children and adults is in the use of inhaled NO therapy for neonatal disease. Although not included in these consensus guidelines, multicenter RCTs have demonstrated the efficacy of low-dose inhaled NO in the treatment of term newborns with PPHN.[128] Clinical efficacy of inhaled NO for the treatment of older patients with other causes of PAH has not been evaluated in randomized clinical trials. The use of type 5 phosphodiesterase inhibitors, such as dipyridamole or sildenafil, have been described in children, but as in adults, data in children are limited to small case series.[129,142]

Pregnancy

The issue of pregnancy in patients with IPAH is important, as many patients with IPAH are women of childbearing age. The hemodynamic demands of pregnancy are substantial and include an increase of 30 to 50% in blood volume, a similar increase in CO, a 10 to 20 beat/min increase in heart rate, an increase in stroke volume, and decreases in both systemic vascular resistance and BP. These hemodynamic changes begin during the first trimester and peak at 20 to 24 weeks of gestation. During labor, there are further increases in CO while the BP also increases with uterine contractions. Immediately postpartum, there are marked volume shifts with the cardiac filling pressures increasing dramatically as a result of decompression of the vena cava and the return of uterine blood into the systemic circulation. The hemodynamic changes associated with pregnancy regress by approximately 6 weeks after delivery. The physiologic changes induced by pregnancy impose a marked hemodynamic stress in women with IPAH, leading to an estimated 30 to 50% mortality rate.[143,144] Due to high maternal and fetal morbidity and mortality rates, most experts recommend effective contraception and early fetal termination in the event of pregnancy.[145]

In addition to the hemodynamic stresses of pregnancy, hormonal changes during and immediately following pregnancy may also be detrimental from a pathophysiologic standpoint. Anecdotal experience suggests that even if a woman successfully delivers a term infant, her PH may progress during pregnancy, and remain worse after pregnancy. Furthermore, there appears to be an increased incidence of infants who are small for gestational age born to women with IPAH, and well as an increased incidence of congenital anomalies.

There are several case reports of successful treatment of pregnant IPAH patients with long-term IV epoprostenol,[146–149] inhaled NO,[150–152] and oral CCBs.[153] However, these cases likely represent the exceptions rather than the rules. In general, current management includes early hospitalization for monitoring, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and dobutamine, as needed. In addition, the use of a pulmonary artery catheter for close hemodynamic monitoring and for titration of vasodilator and cardiotonic therapy has been recommended.

Recommendations for the optimal mode of delivery remains controversial; early concerns of high mortality with cesarean section delivery led to an emphasis on vaginal delivery, and a series of 7 women with severe PH who were successfully delivered by the vaginal route has been described.[154] Successful treatment during cesarean section delivery has also been reported, which may partly be due to the changes in the selection and use of anesthetics.[155]

In a meta-analysis of the outcome of pulmonary vascular disease and pregnancy from 1978 through 1996, Weiss and colleagues[144] reported a maternal mortality rate of 36% in Eisenmenger syndrome, 30% in IPAH, and 56% in secondary PH. Similarly, while acknowledging that data on outcomes are limited, guidelines from the American Heart Association and the American College of Cardiology recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, PH, and Eisenmenger syndrome.

Portopulmonary Hypertension

Patients with chronic liver disease have an increased prevalence of pulmonary vascular diseases compared to the normal population.[156,157] Two forms of pulmonary vascular disease complicate long-term liver disease: the hepatopulmonary syndrome and portopulmonary hypertension. They are quite different, although an occasional patient may have features of both. They both tend to occur in patients with chronic, late-stage liver disease, and each may increase the risk of undergoing liver transplantation.

The hepatopulmonary syndrome is characterized by hypoxemia, which is thought to be due to intrapulmonary shunting. Such shunting may be manifest by the late appearance (after three to five cardiac cycles) of bubble contrast in the left heart. These patients demonstrate low oxygen saturations while breathing room air, and do not increase their saturations as much as would be expected with the administration of 100% oxygen via a partial nonrebreather oxygen mask. They therefore have an increased calculated shunt fraction. They may also demonstrate orthodeoxia, with lower oxygen saturations in the standing position, as opposed to when

lying supine. Treatment is generally supportive, with supplemental oxygen. The syndrome may improve in some patients following liver transplantation.

Portopulmonary hypertension also occurs in patients with chronic, late-stage liver disease. Portal hypertension, occurring with or without hepatic cirrhosis, seems to be required for the development of PH.[158–164] The mechanism underlying the development of PH in patients with portal hypertension is not well understood.[165] Plexiform lesions, characteristic of IPAH,[166] are often found in patients with coexistent cirrhosis and PH.[167]

Portopulmonary hypertension often differs somewhat hemodynamically from IPAH, and these differences may affect the approach to therapy. Patients with portopulmonary hypertension appear to have lower pulmonary arterial diastolic and mean pressures, higher COs, and lower pulmonary and systemic resistances.[158] Later-stage patients may have hemodynamic findings more similar to those of patients with IPAH, and this group may in general have a poorer prognosis, and be at higher risk with attempted liver transplantation. As in all forms of PAH, a thorough evaluation is indicated to exclude other underlying or contributing factors such as chronic recurrent thromboembolic disease, previously undetected congenital heart disease, collagen vascular disease, or prior IV drug abuse (which may be more common among the group of patients with liver disease occurring in association with hepatitis C).

The treatment of portopulmonary hypertension can be challenging and has not been thoroughly studied. Significant PH can substantially increase the risk associated with liver transplantation. It is occasionally possible to make a borderline candidate for liver transplantation an acceptable one through aggressive treatment of their PH. Supplemental oxygen should be used as needed to maintain saturations $\geq 90\%$ at times. Diuretic therapy should be utilized to control volume overload, edema, and ascites. Anticoagulant therapy has not been carefully studied in this population, and should probably be avoided in patients with significant coagulopathy due to impaired hepatic synthetic capability, and in patients at increased risk of bleeding due to gastroesophageal varices. In the absence of a markedly increased CO, and relatively low PVR, patients with mild-to-moderate PH should have acute vasoreactivity assessed in the catheterization laboratory. If such patients demonstrate a favorable acute response to vasodilator, consideration should be given to the cautious introduction of a calcium-channel antagonist. High-dose challenges with calcium-channel antagonists should probably be avoided in these patients, as they may precipitate hepatic failure.

There have been a number of case reports and small case series describing the use IV epoprostenol for treatment of portopulmonary hypertension.[168–172] As in IPAH, the failure to respond acutely to IV epoprostenol does not predict a failure to respond to this agent when administered by long-term IV infusion. It appears as though patients with portopulmonary hypertension respond to long-term IV epoprostenol in a manner somewhat similar to that of patients with IPAH. Interestingly, some patients seem to demonstrate improvement in PH following liver transplantation.[173] This may be particularly true for those with a relatively high CO pretransplantation, which then decreases following successful transplantation. Other patients may have worsening of PH well after transplantation. It may be possible to wean an occasional patient off epoprostenol following liver transplantation. This should probably be done very gradually and under close observation. The development of increasing dyspnea, fluid retention, or fatigue should prompt reevaluation and reinstitution of epoprostenol if indicated. The use of other prostacyclin analogs and methods of drug delivery have not been thoroughly studied in patients with portopulmonary hypertension. A report from Schroeder et al[174] describes the use of inhaled epoprostenol in treatment of portopulmonary hypertension.

Due to its potential for hepatoxicity, most experts would likely recommend avoiding the oral endothelin antagonist bosentan in this population. The use of this agent has not been carefully studied in patients with liver disease.

While some patients who might not otherwise have been candidates for liver transplantation may undergo this procedure with epoprostenol therapy,[175] others may be thought to have such severe disease as to require multiorgan transplantation (such as combined liver and heart-lung transplantation).[176] Such procedures are rarely done, and are generally considered to be very high risk.

HIV Disease

HIV has been implicated in a variety of associated conditions, both infectious and noninfectious. Noninfectious manifestations of HIV infection are more common as a result of longer survival and better prophylaxis against opportunistic infections.[177] PAH is a rare but well-documented complication of HIV infection[178]; > 200 cases have been reported in the literature.[179] The risk of acquiring PAH is higher in HIV-infected individuals than in the general population. In a large case-control study,[180] 3,349 HIV-infected patients observed over a period of 5.5 years

demonstrated a cumulative incidence of PH of 0.57%, resulting in an annual incidence of 0.1%. Compared with the annual incidence of IPAH in the general population of 1 to 2 per million,[181] HIV infection carries a relative risk of PAH > 600.

HIV-related PAH shows similar clinical, hemodynamic, and histologic findings as IPAH. It is not related to the route of HIV transmission, nor to the degree of immunosuppression.[182] In this context, the mechanism of the development of PH remains unclear. As virus or viral DNA is absent in pulmonary endothelial cells,[183,184] an indirect action of virus through second messengers such as cytokines,[183] growth factors,[183] or endothelin[185] is strongly suspected. This hypothesis is reinforced by the presence of perivascular inflammatory cells in HIV-associated PAH.[186,187] In addition, because this complication affects only a minority of HIV-infected patients, one could hypothesize that genetic factors play an important role in its development. The absence of germ-line bone morphogenetic protein receptor II mutation in a subset of 30 tested patients with HIV-associated PAH suggests that other susceptibility factors are involved.[188] Mortality of patients with HIV-associated PAH is mainly related to PH itself, rather than to other complications of HIV infection.[182] PAH is an independent predictor of mortality in these patients.[180]

In HIV-associated PAH, therapeutic options are more limited than for IPAH; lung transplantation is not advisable in this population, oral anticoagulation is often contraindicated because of frequent hemostasis abnormalities and potential drug interactions between HIV medications and warfarin, and long-term beneficial effect of CCBs has never been reported in this PAH subgroup. To date, no placebo-controlled randomized trial of prostacyclin or novel therapies have been carried out in HIV-associated PAH. One uncontrolled open study[189] of six patients with severe HIV-associated PAH suggests that continuous infusion of epoprostenol might be effective in improving functional status and hemodynamics both short-term and long-term (follow-up ranged from 12 to 47 months). The role of highly active antiretroviral therapy in the management of HIV-associated PAH remains to be established. In the Swiss cohort, a beneficial effect on pulmonary hemodynamics was observed in patients treated nucleoside reverse transcriptase inhibitors.[180] A single case report[190] of long-term hemodynamic improvement with highly active antiretroviral therapy, without the associated use of any vasodilator agents, has been published. Lastly, in a large monocentric case series of 82 patients,[188] univariate analysis indicated that CD4 count (> 212 cells/μL), combination antiretroviral therapy (CART), and the use epoprostenol

infusion, were associated with a better survival. On multivariate analysis, only CD4 lymphocyte count was an independent predictor of survival, presumably because CART and epoprostenol infusion were strongly linked in this study population.

In summary, uncontrolled studies suggest that patients with severe HIV-associated PAH should be considered for long-term infusion of epoprostenol in association with CART. However, epoprostenol infusion, as well as less-invasive novel therapies (prostacyclin analogues, endothelin-receptor antagonists, and phosphodiesterase type 5 inhibitors) should be evaluated in this patient population in RCTs.[191]

Recommendations

15. **In children with PAH, the recommendations for medical therapy (other than anticoagulation) in adults also apply.** Quality of evidence: low; net benefit: substantial; strength of recommendation: B.
16. **Children with PAH:**
    a. **with right-heart failure or with a hypercoagulable state should receive anticoagulation with warfarin.** Level of evidence: expert opinion; net benefit: intermediate; strength of recommendation: E/B.
    b. **without right-heart failure or a hypercoagulable state may receive anticoagulation with warfarin; for children < 5 years of age, lower target INRs 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.

Summary

The treatment of PAH is advancing rapidly. Multicenter RCTs have provided a basis for evidence-based practice. The treatment algorithm (Fig 1) attempts to summarize the current approach to therapy for PAH. Recommendations regarding therapy obviously need to be applied in light of the individual patient's specific situation. 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 is strongly recommended that consideration be given to referral of patients with PAH to a specialized center. Further research and well-controlled clinical trials should lead to further improvements in the treatment of this very challenging disease.

SUMMARY OF RECOMMENDATIONS

1. **Patients with IPAH should undergo acute vasoreactivity testing using a short-acting agent such as IV epoprostenol, adenosine, or inhaled NO.** 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 mPAP of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or unchanged CO), should be considered candidates for a trial of 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 PAP of at least 10 mm Hg to ≤ 40 mm Hg, with an increased or unchanged CO), 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; 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; recommendation: E/A.

10. **Patients with PAH in functional class II who are not candidates for, or who have failed, CCB therapy may benefit from treatment. However, limited data are available, and no specific drug can be recommended. Enrollment in clinical trials is encouraged.** Level of evidence: expert opinion; benefit: intermediate; grade of recommendation: E/B.

11. **Patients with PAH 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).** Level of evidence: good; benefit: substantial; grade of recommendation: A.
    b. **IV epoprostenol.** Level of evidence: good; benefit: substantial; grade of recommendation: A.
    c. **Subcutaneous treprostinil.** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.
    d. **Inhaled iloprost.** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.
    e. **Beraprost.** Level of evidence: good; benefit: conflicting; grade of recommendation: I.

12. **Patients with PAH 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 patients with PAH and functional class IV include, in no hierarchical order:**
    a. **Endothelin-receptor antagonists (bosentan).** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.

b. **Subcutaneous treprostinil.** Level of evidence: fair; benefit: intermediate; grade of recommendation: B.

c. **Inhaled iloprost.** Level of evidence: low; benefit: small; grade of recommendation: C.

14. **In patients with PAH who have failed or are not candidates for other available therapy, treatment with sildenafil should be considered.** Level of evidence: low; benefit: intermediate; grade of recommendation: C.

15. **In children with PAH, the recommendations for medical therapy (other than anticoagulation) in adults also apply**. Quality of evidence: low; net benefit: substantial; strength of recommendation: B.

16. **Children with PAH:**

a. **with right-heart failure or with a hypercoagulable state should receive anticoagulation with warfarin.** Level of evidence: expert opinion; net benefit: intermediate; strength of recommendation: E/B.

b. **without right-heart failure or a hypercoagulable state may receive anticoagulation with warfarin; for children < 5 years of age, lower target INRs 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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