Pulmonary Arterial Hypertension Treatment Guidelines

New Answers and Even More Questions

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Energy and persistence conquer all things.

Benjamin Franklin

I vividly remember my first patient with pulmonary arterial hypertension (PAH) during my internship in 1999. We admitted a young woman with pulmonary hypertension, clearly miserable from right-sided heart failure. Although she had been followed in our pulmonary hypertension clinic, there was little to offer her until she clearly required the only medication that was known to be efficacious in patients with PAH at that time: IV epoprostenol.¹ Within a few days of starting therapy, she was a new person: walking through the hall, heart failure resolved, and ready to go home to her family. The drug was unquestionably life saving, but at the same time, it was bittersweet that the only therapy available then required continuous infusion for the rest of her life and had many undesirable side effects.

In 1999, PAH treatment guidelines would have been very brief: Use supportive therapy until the patient is very sick, then start IV epoprostenol. Now, 15 years later, we have eight different US Food and Drug Administration-approved medications for PAH, including oral options with minimal side effects. We have evidence that early

therapy with these well-tolerated drugs improves outcomes in PAH.² And, importantly, we are beginning to study pathobiology and potential treatments for the other non-PAH causes of pulmonary hypertension, such as that associated with left-sided heart disease (World Health Organization [WHO] group 2), chronic lung disease (WHO group 3), and chronic thromboembolic pulmonary hypertension (WHO group 4).³⁻⁶ This wealth of new data and treatment options produced through hard work, advancing science, and new drugs has raised many questions about the best treatment of PAH today. To address these new concerns, Taichman et al⁷ have appraised the available data on PAH and produced the CHEST guidelines published in this issue of *CHEST* (see page 449). The authors of the guidelines reviewed 8,526 citations on the topic and took a rigorous approach to the assessment of the strength of each piece of evidence used to substantiate the suggested therapy.

What do these 79 treatment recommendations tell us and how do they differ from older guidelines? First, and perhaps most importantly, the authors recommend that, whenever possible, patients with PAH be evaluated promptly at a center with experience in the diagnosis of pulmonary hypertension, prior to the initiation of therapy. This key recommendation should increase the likelihood that the cause of pulmonary hypertension will be assigned appropriately and that only patients with PAH receive PAH-directed care. Differentiation of PAH (WHO group 1) from other forms of pulmonary hypertension (groups 2-5) is challenging for even experienced physicians. In this document, treatment recommendations are all aimed specifically at patients with PAH; they do not apply to any other category of pulmonary hypertension and, because some PAH-approved therapies may be harmful in other forms of pulmonary hypertension, making an accurate diagnosis is imperative.⁸

In initial selection of PAH therapy, the authors still recommend stratification by functional class. Continued monitoring is recommended for functional class I patients. Vasoreactivity testing during right-sided heart catheterization at an expert center is recommended, and, in patients meeting published hemodynamic criteria,⁹ calcium channel blocker therapy is recommended. All other recommendations apply to those patients who are not acutely responsive to vasodilators.

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For patients who are functional class II or III without evidence of rapid disease progression or poor prognostic markers, oral monotherapy with one of the three Food and Drug Administration-approved classes of oral medications (endothelin receptor antagonist, phosphodiesterase inhibitor, or soluble guanylate cyclase stimulator) is recommended. Prostaglandin therapy is recommended for patients who are functional class III with rapid progression or poor prognostic markers (parenteral prostaglandin) or progression despite one or two oral therapies (parenteral or inhaled prostaglandin), but not in patients who are functional class II without these markers. In patients who are functional class IV, parenteral prostaglandin is suggested as initial therapy.

An addition to prior treatment guidelines^{10,11} are specific recommendations for continued care of patients with PAH already on established therapy. In this circumstance, the authors recommend evaluation at expert centers as well as initiation of a second agent of a different class for functional class III or IV, generally inhaled or parenteral prostaglandin, in appropriate patients. Three classes of PAH-specific therapy are recommended for patients who are functional class III or IV with deterioration on two classes of medication.

Major uncertainties, however, persist in the management of PAH. First, the guidelines address only adult patients with PAH and none of the other more common causes of pulmonary hypertension, such as that associated with left-sided heart disease, parenchymal lung disease, or chronic thromboembolic pulmonary hypertension. These guidelines do not address children with PAH, in whom the disease is not well studied and for which there may be different causes, responses to therapy, and side effects. Second, despite >8,500 citations on this topic, the authors were able to assign an evidence grade to nine recommendations only. The remaining 70 were consensus-based recommendations. This highlights the dearth of high-quality, replicated clinical trials in PAH. Third, management of patients who are functional class I consists essentially of a “watchful waiting” approach. Although these patients are rare, enhanced screening in at-risk populations, such as those with scleroderma or those who are known PAH-associated mutation carriers, will identify increasing numbers of patients with early-stage PAH. Determining when and how to treat this group will require better mechanistic markers of progressive disease as well as perhaps extended drug trials to test efficacy in preventing symptomatic PAH. Such markers, which, it is hoped,

will be identified by thorough, rigorous phenotyping, may also allow a more informed selection of therapy for an individual symptomatic patient with PAH; this is the so-called “personalized medicine.” Finally, the new guidelines classify all PAH medications as improving 6-min walk distance or functional class, or reducing time to clinical worsening. Notably absent are any therapeutics for the failing right ventricle. Right-sided heart failure is the major cause of death in patients with PAH,¹² suggesting that the development of right ventricular-specific therapies should be a major priority in upcoming years. This will require understanding the determinants of right-sided heart structure and function in health and disease and the best tools for assessment of right-sided heart failure. These are all areas of active investigation and should bear fruit in future treatments of PAH.

How do these recommendations apply to patients who are seen outside specialized centers? Key insight comes from an article by George et al,¹³ also included in this issue of *CHEST* (see page 476). This study examined mortality data from the National Vital Statistics System and hospital discharge data from the National Hospital Discharge Survey. The authors identified a rapid acceleration in pulmonary hypertension-associated mortality and hospital discharge rates. Closer examination of their data indicates that these changes are driven largely by patients who are older than typical patients with PAH. In fact, death rates for pulmonary hypertension were highest in those aged ≥ 85 years, with a 65% increase in the decade studied. In 2010, 21,292 patients who died had a pulmonary hypertension code on their death certificate; 77% of these patients were > 65 years at the time of death. Data on pulmonary hypertension cause is difficult to discern in this article because of differences in clinical classification and *International Classification of Diseases* coding, but Fig 1 in their article suggests that higher pulmonary hypertension mortality rates are driven by a rapid rise in so-called secondary pulmonary hypertension (presumably groups 2-5). Hospitalization rates followed a similar pattern. Recent work has shown that PAH is a rare diagnosis in patients aged ≥ 65 years, and other forms of pulmonary hypertension are much more common in patients who undergo a thorough evaluation for pulmonary hypertension cause.¹⁴ Data from George et al¹³ are, thus, best interpreted as showing that increasing mortality and hospital discharge data are largely driven by patients with pulmonary hypertension due to lung disease, left-sided heart failure, chronic thromboembolic

pulmonary hypertension, or a mixture of these conditions. The work of George et al¹³ shows that the bulk of pulmonary hypertension evaluated and treated by community providers is likely not addressed by the PAH-directed guidelines published in this issue.

The articles by George et al¹³ and Taichman et al⁷ in this issue reveal the best of our accomplishments in PAH and the ongoing challenges that face patients with pulmonary hypertension and their providers. In PAH, advancing mechanistic insight, therapies directed specifically at the right ventricle, new trial designs and end points, and the hope of personalized medicine will shape future guidelines from CHEST and other organizations. In all other forms of pulmonary hypertension, we are just beginning a journey. It is hoped that improved understanding of pathobiology will drive new treatments and will allow inclusion of groups 2 to 5 pulmonary hypertension in future recommendations. Science is like an endurance sport, with major accomplishments in the past 2 decades in PAH in particular, but a long and hilly road still lies ahead to effectively treat all forms of pulmonary hypertension.

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A New Standard of Care for Critically Ill Patients With Cancer

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Several million patients worldwide live with cancer.^{1,2} Possible outcomes are complete cancer eradication; cancer control using chemotherapy, targeted therapies, or both; and palliative treatments that may both prolong life and increase quality of life.³ All patients with cancer are at a high risk for pulmonary disease due to infections, infiltration by malignant cells, or treatment toxicities.⁴ Severe respiratory episodes, usually with acute respiratory failure, affect up to 40% of patients with cancer.⁵ Mechanical ventilation (MV), whether invasive or noninvasive ventilation (NIV), must be considered the standard of care for consenting patients who are not bedridden and who are receiving curative or palliative chemotherapy. This statement indicates a major change

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