

Methodology and Grading for Pulmonary Hypertension Evidence Review and Guideline Development

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Abstract

The American College of Chest Physicians assembled a multidisciplinary, geographically diverse panel of experts in the treatment of pulmonary hypertension to develop clinically relevant practice guidelines for the diagnosis and treatment of pulmonary hypertension in its many variations. That group of experts produced recommendations covering five topic areas, each related to a distinct set of patient management decisions. This article describes the approach used to develop the guidelines, including identifying, evaluating, and synthesizing the evidence, assessing the strength of evidence pertinent to individual guidelines, and grading guideline recommendations.

Key Words:

Clinical Practice Guidelines

Evidence-based Medicine

Pulmonary Hypertension

Abbreviations:

ACCP	American College of Chest Physicians
FCCP	Fellow of the American College of Chest Physicians
PAH	Pulmonary Arterial Hypertension
PPH	Primary Pulmonary Hypertension
QRG	Quick Reference Guide

Introduction

The American College of Chest Physicians (ACCP) Health and Science Policy committee, with the endorsement of the Board of Regents, selected Pulmonary Arterial Hypertension (PAH) as a priority for evidence-based guideline development in 2001. Ten years ago a consensus panel on Primary Pulmonary Hypertension (PPH) was formed which provided a well-received and concise general review of diagnosis, management, and pathobiology of PPH. The purpose of the current project is not only to update the former consensus statement, but also to make a guideline that is explicitly evidence-based.

An expert panel was selected to synthesize these results and write recommendations based on the current knowledge of diagnostic and treatment modalities for PAH. The Duke University Center for Clinical Health Policy Research was selected to review and summarize the current evidence in this area. The resulting evidence-based recommendations are targeted toward an audience of cardiologists, pulmonologists, rheumatologists, and primary care physicians, as well as other health care providers who treat PAH.

Panel Selection and Composition. Dr. Rubin, of the University of California, San Diego, serves as the chair of this international panel of 19 pulmonary hypertension experts representing five medical specialties. They were both members and nonmembers of the ACCP. Representatives from other medical and patient advocacy associations were invited to join the panel (including the American College of Cardiology, American College of Rheumatology, and the Pulmonary Hypertension Association). These experts convened on several occasions, including the final panel conference in September 2003, in which they

deliberated over the final recommendations and grading of the current state of the evidence, benefits to the patient, and the recommendations.

Scope. The panel chose the following topics for review and analysis:

- Screening, Early Detection, and Diagnosis
- Medical Therapies
- Surgical Therapies
- Prognosis
- Sleep Apnea

Screening, as opposed to monitoring, at risk but asymptomatic individuals included patients with HIV, scleroderma, portal hypertension, family members, and those being evaluated for liver transplants. There is also some literature on genetic screening. Diagnosis applies to patients suspected of having pulmonary hypertension and would be identified by history, physical exam, electrocardiography, chest radiography, V/Q scan, arteriography, magnetic resonance imaging, CT scanning, pulmonary function testing, cardiac catheterization, and serology markers.

Therapies were divided into medical and surgical. Medical therapies included supplemental oxygen, diuretics, digoxin/inotropics, anticoagulants, calcium channel blockers, ACE-inhibitors, prostanoids, L-arginine, endothelin receptor antagonists, phosphodiesterase inhibitors (PDESI), and nitrous oxide. Surgical therapies were restricted to transplantation, pulmonary thromboendarterectomy, and atrial septostomy.

Since sleep apnea may be an independent risk factor for PAH, treatment of sleep apnea was reviewed, analyzed, and documented separately. Prognosis has changed dramatically over the last decade because of improved therapies. It was deemed important to discuss the

parameters that predict prognosis and how they can be utilized in treatment choice decisions.

The scope of the guideline included idiopathic pulmonary artery hypertension and secondary pulmonary hypertension including collagen vascular disease, scleroderma, HIV-associated pulmonary hypertension, portal hypertension associated with PH, chronic thromboembolic disease, and COPD and other parenchymal lung disease. Eisenmenger's syndrome and other forms of congenital heart disease would be included but not cardiac disease, *eg.* left-sided heart failure, valvular heart disease, or high altitude PAH.

Evidence Review. The Center for Clinical Health Policy Research at Duke University identified and evaluated evidence on each of the five topics, working with the panel to formulate key questions suitable for systematic literature synthesis.

To address the questions, we conducted computerized searches of the MEDLINE bibliographic database from 1992 to October 2002 (see Appendix). We searched using the term “hypertension, pulmonary”. We limited the search 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 consulted with clinical experts to identify relevant studies missed by the search strategy or published before 1992.

Two physicians (one with methodological expertise and one with content area expertise) reviewed the abstracts of candidate articles and selected a subset for review in full text. Full-

text articles were again reviewed by two physicians to determine whether they were study reports or review articles and were pertinent to at least one of the key questions. The selection criteria differed for each topic. The revised questions and topic-specific search terms and selection criteria are described in detail in the subsequent chapters devoted to each topic.

Development. The development was led by an executive committee including the chair (LR), the leader of the methodology support group (DM), and ACCP project manager (SZL), which supervised the progress of the project. The executive committee directed the guideline development process, methodological issues, panel composition, structure of the final document, and activities of the writing committees. Each writing committee, led by a group leader who served as primary author and editor of that chapter, conferred with the methodology team on inclusion/exclusion criteria, relevant research questions, and important literature that was not readily identified. These individuals continue with their responsibilities to assist in the development of the implementation tools (*eg*, Quick Reference Guide (QRG) in print and PDA format and slide presentations for physician and other healthcare practitioners' educational programs).

Funding and Conflicts of Interest. Funding for both the evidence reviews and guideline development was provided through an unrestricted educational grant from GlaxoSmithKline, Texas Biotechnology Corporation, and Actelion Pharmaceuticals US. Representatives from these companies were not granted right of review nor were they allowed participation in any portion of the guideline development.

All conflicts of interest within the preceding 5 years were required to be disclosed by all panelists, including those who did not have writing responsibilities. These are documented in the guideline supplement.

Grading. The recommendations were graded using the ACCP Health and Science Policy Grading System, as outlined below, which is based on two components, the quality of the evidence and the net benefit of the diagnostic or therapeutic procedure. The evidence is graded according to the methodologies used in the included studies. The net benefit is based on the benefit to the patient population as defined in the recommendation and not for any specific individual patient. Both components are listed after each recommendation but their interaction defines the strength of the recommendation, refer to the chart below.

Quality of the Evidence

Good - Evidence is based on good randomized controlled trials or meta-analyses

Fair - Evidence is based on other controlled trials or RCT with minor flaws

Low - Evidence is based on non-randomized, case-control, or other observational studies.

Expert opinion – Evidence is based the consensus of the carefully selected panel of experts in the topic field. There are no studies that meet the criteria for inclusion in the literature review.

Net Benefit

Substantial

Intermediate

Small/Weak

None

Conflicting

Negative

Strength of Recommendation

- A - Strong recommendation
- B - Moderate recommendation
- C - Weak recommendation
- D - Negative recommendation
- I - No recommendation possible (Inconclusive)
- E/A - Strong recommendation based on expert opinion only
- E/B - Moderate recommendation based on expert opinion only
- E/C - Weak recommendation based on expert opinion only
- E/D - Negative recommendation based on expert opinion only

Relationship of Strength of the Recommendations Scale

To Quality of Evidence and Net Benefits

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

When the evidence was insufficient for evidence-based recommendations, the panel used informal group consensus techniques to develop recommendations based on the expert opinion of the panel. With every member of the panel attending the final conference, the expert-based opinions are truly representative of geographically diverse and multispecialty inclusive practice patterns of the complete panel. The only defining characteristic that was not diverse was that most of the panel members practiced in large centers with high volume experience in treating patients with pulmonary hypertension.

Validation. The writing groups and the executive committee of the panel extensively reviewed each chapter during the writing process. The final conference provided an opportunity for the entire panel to review the latest drafts. Following final revisions and one final review by the executive committee, each chapter of the guidelines was reviewed and approved by the ACCP Health and Science Policy Committee, the ACCP Pulmonary Vascular NetWork, and then by the ACCP Board of Regents. The guidelines have not been field-tested.