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Official publication of the American College of Chest Physicians

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Chest 2010;137;85S-94S
DOI 10.1378/chest.09-2816

ISSN:0012-3692

CHEST Supplement

PULMONARY VASCULAR DISEASE: THE GLOBAL PERSPECTIVE

Worldwide Physician Education and Training in Pulmonary Hypertension

Pulmonary Vascular Disease: The Global Perspective

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Pulmonary hypertension (PH) affects >25 million individuals worldwide and causes premature disability and death for many. The diagnosis and treatment of PH have advanced dramatically through the development of a clearly defined diagnostic classification, an evidence-based treatment algorithm for adults with pulmonary arterial hypertension using life-saving medications, and life-saving surgical procedures. However, worldwide education and training of physicians has lagged behind advances in the management of PH. Expertise in the diagnosis and management of PH is uncommon, even though physicians receive training on PH during their graduate and postgraduate education. Advances in worldwide physician education and training in PH will require substantial organization and work. Organizations working in this field will need to work collaboratively to maximize funding for education and to optimize the achievement of educational goals. Political, economic, and cultural barriers must be identified and overcome as part of any strategic plan. Global education should include training objectives for generalist, non-PH specialist, and PH specialist physicians. ***CHEST 2010; 137(6)(Suppl):85S–94S***

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

The issue of global education and training of pulmonary and cardiology physicians is hardly new or limited to pulmonary hypertension (PH). In 1966 Donato Alarcón[1] summarized trends in medical education that were imposed by advances in the diagnosis and treatment of respiratory and cardiovascular diseases. Alarcón addressed the importance of informing general practitioners of the dramatic advances in the treatment of cardiovascular diseases at specialized centers. Alarcón also recognized that TB mortality rates differed by country, with substantially higher death rates in countries such as Chile or Portugal where physicians, at that time, lacked training and resources to diagnose and treat TB. Alarcón stated "If we want to eradicate tuberculosis, we must teach young doctors to use three major means: roentgenography, tuberculin…, and early treatment." Alarcón wisely noted "It is also extremely important to emphasize the necessity of teaching [about] diseases which are largely replacing tuberculosis in epidemiologic frequency…."[1]

Pulmonary hypertension, leading to right ventricular failure, is an important cause of death and disability all over the world.[2-6] The management of PH has advanced dramatically during the past 25 years.[7-15] In

Manuscript received November 25, 2009; revision accepted February 13, 2010.

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DOI: 10.1378/chest.09-2816

this regard, PH offers many of the same challenges and opportunities for global education and training of physicians that advances in the treatment of TB and cardiovascular disease did > 40 years ago. Worldwide education and training of physicians to suspect, confirm, and differentiate the causes of PH, and to initiate appropriate therapy, will require a global plan and substantial effort. Political, economic, and cultural barriers must be identified and overcome as part of any strategic plan.[6,16]

Pulmonary hypertension is a chronic cardiopulmonary disorder. Current lower estimates of incidence suggest that one to three cases of idiopathic pulmonary arterial hypertension (PAH) and two to five cases of associated PAH are diagnosed per million inhabitants each year in Europe[17,18] and North America.[19] Current prevalence estimates of PH are limited for populations at large as well as for individuals diagnosed with conditions commonly associated with PH. The recent consensus statement of the fourth World Symposium on Pulmonary Hypertension[20] represents a necessary step for global estimates of the prevalence of PH. As shown in Table 1, five main subcategories embrace a large group of chronic systemic, cardiac, and pulmonary disorders. The breadth of illnesses associated with PH suggests that the worldwide impact of PH is quite formidable. Registries, such as the French and Scottish registries, have provided lower limits for the estimated prevalence for one diagnostic subgroup (group 1 PAH) of 15 per million adults[17] and 26 per million adults, respectively.[18] Estimates of the prevalence of diagnostic group 1 PAH associated with underlying diseases vary substantially from one region of the world to another because of wide variations in the prevalence of associated disorders, such as connective tissue diseases,[19,21,22] portal hypertension,[19,23-25] schistosomiasis,[26] hemolytic anemia,[27] and HIV infection.[28,29,30] In The Netherlands, approximately 9 per million adults have PAH associated with scleroderma.[31] Global estimates of the prevalence of other diagnostic group 1 subcategories are not available at this time. Prevalence estimates for PH owing to left-sided heart disease, lung diseases and/or hypoxia,[32,33] chronic thromboembolism,[19,34] and sleep-disordered breathing[35] are also quite limited. Recently initiated registries in Saudi Arabia, China, and India[36-38] may begin to add to our understanding of the global prevalence of PH.

Like TB, PH wears many faces around the world. Although idiopathic pulmonary arterial hypertension and heritable PAH are relatively uncommon, many conditions associated with PH are common in developing countries. HIV infection is a global epidemic estimated to affect 33.2 million people, with high prevalence in sub-Saharan Africa (Fig 1).[39] If estimates are correct that 0.5% of HIV-infected individuals have concomitant PAH, then approximately 1.7 million individuals have PAH associated with HIV infection. Schistosomiasis (diagnostic group 1) is another face of PAH in sub-Saharan Africa, South America, parts of China, and Middle Eastern countries (Fig 2).[40] If estimates are correct that 10 million individuals have hepatosplenic schistosomiasis and portal hypertension and that 4.6% of such patients have PAH,[18,20,26] then PAH associated with schistosomiasis affects approximately 460,000 individuals. Hemolytic anemias, such as sickle cell anemia, (diagnostic group 1) represent yet another face of PH seen predominantly in Africa and Asia (Fig 3).[41] Approximately 250,000

Table 1—*Diagnostic Classification of Pulmonary Hypertension*

1. PAH
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
     - 1.2.1. BMPR2
     - 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
     - 1.2.3. Unknown
   - 1.3. Drug and toxin induced
   - 1.4. Associated with
     - 1.4.1. Connective tissue diseases
     - 1.4.2. HIV infection
     - 1.4.3. Portal hypertension
     - 1.4.4. Congenital heart diseases
     - 1.4.5. Schistosomiasis
     - 1.4.6. Chronic hemolytic anemia
   - 1.5. Persistent PH of the newborn
   - 1.6. PVOD and/or PCH
2. PH owing to left-sided heart disease
   - 2.1. Systolic dysfunction
   - 2.2. Diastolic dysfunction
   - 2.3. Valvular disease
3. PH owing to lung diseases and/or hypoxia
   - 3.1. COPD
   - 3.2. Interstitial lung disease
   - 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4. Sleep-disordered breathing
   - 3.5. Alveolar hypoventilation disorders
   - 3.6. Chronic exposure to high altitude
   - 3.7. Developmental abnormalities
4. CTEPH
5. PH with unclear multifactorial mechanisms
   - 5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
   - 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenic protein receptor type 2; CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis; PH = pulmonary hypertension; PVOD = pulmonary venoocclusive disease. Reprinted with permission from Simonneau et al.[20]

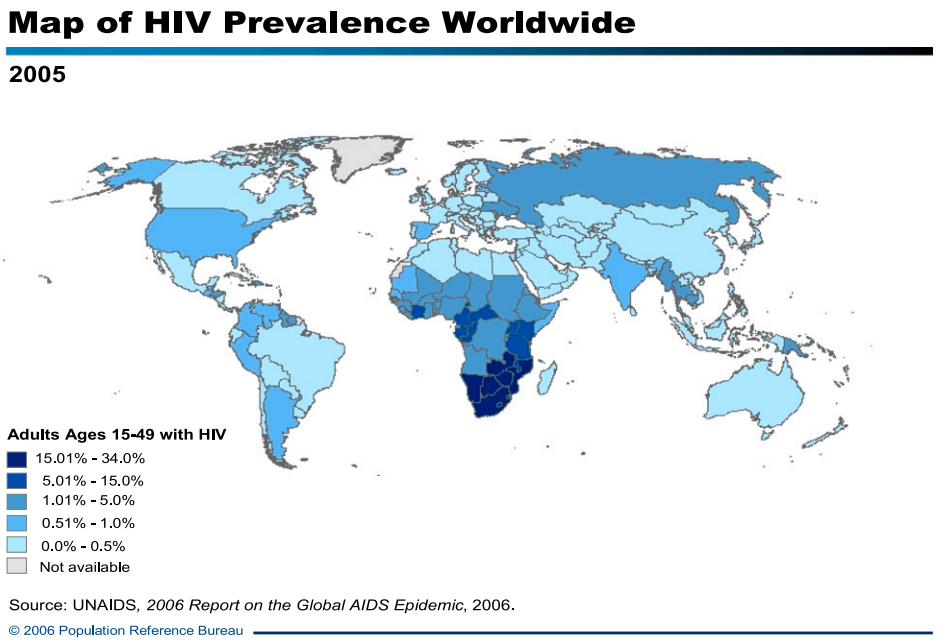

FIGURE 1. The prevalence of World Health Organization diagnostic group 1 pulmonary arterial hypertension (PAH) varies throughout the world because of wide differences in the prevalence of associated disorders. PAH is associated with HIV infection. As shown, 15% to 34% of adults in sub-Saharan Africa are infected with HIV, whereas $<1\%$ of adults are infected with HIV in most other parts of the world. (Reprinted with permission from UNAIDS.[39])

children are born with homozygous sickle cell anemia every year,[42] yet the worldwide prevalence of PAH associated with sickle cell anemia remains unknown. In the United States and other developed nations, PH due to left-sided heart disease (diagnostic group 2) is common. Furthermore, reports indicate that in some parts of the world PH occurs in 70% of patients afflicted by rheumatic heart disease,[43] and that rheumatic heart disease remains a major public health problem in the developing world.[44] In addition, PH affects a large number of patients with chronic lung diseases or hypoxemia or both (diagnostic group 3). For example, chronic mountain sickness is the face of PH for many of the 25 million individuals who live $>2{,}500$ m above sea level in remote areas of Tibet, Peru, and Bolivia.[45,46] Chronic thromboembolic PH (CTEPH) (diagnostic group 4) is also common throughout the world because many patients who

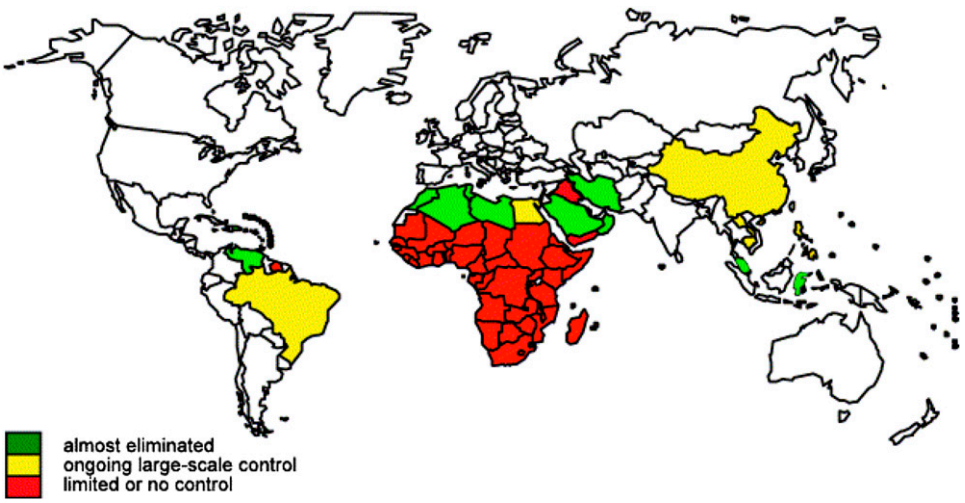

FIGURE 2. Schistosomiasis is a common cause of pulmonary arterial hypertension. Like most parasitic diseases, schistosomiasis prevalence derives from poor living conditions. Schistosomiasis remains poorly controlled in sub-Saharan Africa. Improved control has occurred in much of the Middle East, Asia, and South America. (Reprinted with permission from Engels et al.[40])

suffer acute pulmonary embolism each year (regardless of whether the pulmonary embolism is diagnosed at the time of the embolic events or not) have residual PH.[34]

The burden of PH is likely to grow in the United States as the post- World War II "baby boomers" age and develop PH because of chronic respiratory disorders and left ventricular diastolic dysfunction. However, this will be dwarfed by the exploding incidence and prevalence of chronic lung and heart diseases in other parts of the world.[47]

Diagnosis, treatment, and understanding of PH have advanced rapidly over the past 2 decades. International groups of experts have published consensus documents to define the diagnostic classification, the evolving understanding of pathobiology, and the management of PH.[20,48-61] These documents focus on adult patients with PH based on a greater knowledge base for these patients. Diagnostic and treatment approaches for children with PH have been extrapolated from adult guidelines based on the similarities clinically and pathologically between children and adults with various forms of PH.

The first therapy for PAH was approved in 1995. Since then, an additional 10 drugs have been approved. These newer therapies have improved functional class and exercise capacity as assessed by 6-min walk test performance and cardiopulmonary exercise testing, and have prolonged the time to events that mark clinical worsening, such as death, lung transplantation, and hospitalization for right ventricular failure (ie, reduced overall morbidity and mortality caused by PH).[8,9,11,15,62-67] Furthermore, partial and complete reversal of severe PH is possible, underscoring the societal obligation to train physicians in the diagnosis, assessment, and treatment of PH.[10,68,69]

Education and training have not kept pace with the rapid advances in diagnosis and treatment of PH. Expertise in PH is uncommon, even though physicians receive training and exposure to PH during their graduate and postgraduate education. Delayed diagnosis and treatment of PH are net effects of the gap between advancing knowledge and limited educational opportunity. Recent data provide support for better outcomes with earlier diagnosis and earlier initiation of effective therapies.[70]

Current State of Physician Education and Training in Pulmonary Hypertension

Postgraduate education and training related to PH remain fragmented in the United States. Internal medicine and pediatric residency programs are

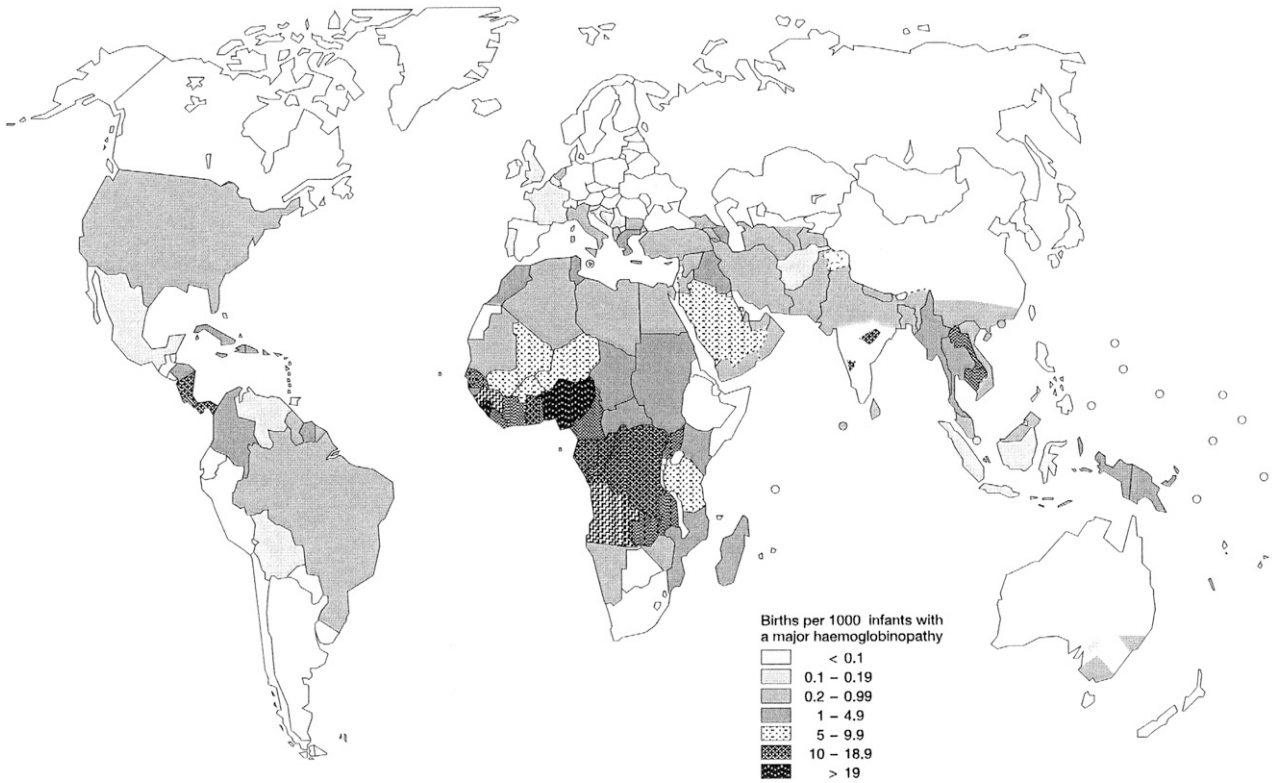

Figure 3. Hemoglobinopathies, such as sickle cell anemia, are prevalent in sub-Saharan Africa and Asia. These disorders are associated with diagnostic group 1 pulmonary arterial hypertension. (Reprinted with permission from the World Health Organization.[41])

overwhelmed by the breadth of problems and knowledge as well as insufficient time for education.[71] Similar challenges confront adult and pediatric specialty training programs (eg, cardiology and pulmonology), which are natural training environments for the development of expertise in PH. The American College of Graduate Medical Education requires formal instruction, clinical experience, and demonstrated competence in evaluation and management of PH. Multisociety task force recommendations for competency in pulmonary medicine include expectations for expertise and proficiency in the assessment and management of PH.[72] However, the majority of pulmonary training programs in the United States offer little or no formal training in echocardiography, limited training in right-sided heart catheterization to evaluate PH, and limited exposure to patients with PAH treated with advanced therapies, such as continuous intravenous epoprostenol. Cardiology fellowships routinely offer training in right-sided heart catheterization and echocardiography, but exposure to patients with the full spectrum of PH (eg, CTEPH, PAH, and life-saving therapies such as epoprostenol or pulmonary endarterectomy) are limited. Individual cardiology or pulmonary trainees in the United States may use protected time to gain additional training and experience related to PH. The picture appears similar throughout the developed world, whereas education and training opportunities relevant to PH in less-developed regions of the world are even more constrained. This is compounded by the lack of cardiac surgery training in less-developed countries where children born with congenital heart disease are not afforded surgical repair and develop severe, inoperable PAH. Indeed, human and economic resources may not support educational goals for competency in diagnosing and treating PH in some regions of the world.

Currently there are a few opportunities for physician-scientist education and training directly related to the pathobiology of PH. The Pulmonary Hypertension Association funds fellowship awards for the development of investigators in the field of PH. In addition, a number of institutions offer short- or long-term fellowship experiences that focus on diagnosis, treatment, and investigation of pulmonary hypertension.

Model for Worldwide Education and Training in Pulmonary Hypertension

We propose a three-tiered model for worldwide physician education and training in PH (Fig 4). Such a model allows for graduated education and training based on the role that the physician will play, and allows for physicians to differentiate based on their interests and the needs of their communities. PH specialist physicians focus their careers on the diagnosis and treatment of PH. These physicians evaluate and treat large numbers of patients with PH at tertiary referral centers where they are often integrated with advanced programs (eg, lung transplantation). Expertise in PH is a common characteristic of PH specialist physicians. However, PH specialist physicians often possess unique expertise in one or more disciplines, such as cardiology or respiratory medicine, and their PH centers often integrate additional expertise (eg, heart and lung imaging, cardiovascular surgery, nursing) in order to achieve enhanced care for patients with PH. General specialist physicians have training in relevant specialties, such as pulmonology and cardiology, but they do not limit their efforts to the care of patients with PH, and they often collaborate with PH specialists in the care of these patients. Generalist physicians have received training in primary care, such as internal medicine, pediatrics, or family medicine, or practice in emergency rooms or ambulatory clinics. Generalist physicians often encounter patients with PH when they first seek medical attention,[73] and they must recognize symptoms, signs, and laboratory abnormalities that suggest PH. Generalist physicians must suspect PH in individuals with vague, slowly insidious symptoms, especially breathlessness and fatigue. Generalist physicians often will collaborate with general specialists and PH specialists in the care of patients with PH. Generalist, general specialist, and PH specialist education and training programs could all benefit from clear definitions of PH-relevant learning objectives and competencies.

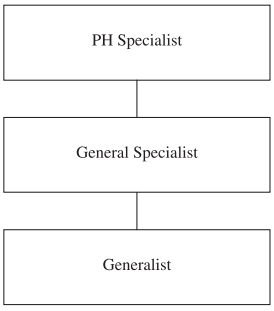

FIGURE 4. A three-tiered model of generalist physicians, general specialists (eg, cardiologists and pulmonologists), and PH specialists provides a framework for worldwide physician education and training in pulmonary vascular diseases. This model allows responsible leaders to allocate and identify resources to match the needs of their countries. It also allows physicians to seek training commensurate with the role that the physician will play, educators to develop curricula, and certifying organizations to define program requirements for certification and credentialing. PH = pulmonary hypertension.

What Are Core Competencies for Pulmonary Hypertension Education and Training?

Just as Alarcón[1] defined the essentials for global education necessary to diagnose and treat TB, it is incumbent for the PH community to define core competencies for clinicians to confront the global burden of PH. Modern evidence-based educational guidelines suggest that education and training should include a curriculum that engages learners at all levels.[74] Educational experiences should include clear learning objectives, engagement in educational activities (eg, data interpretation), and focused repetitive practice with monitoring and correction of errors by direct feedback. Furthermore, educational and training programs should adopt recommendations for continuing education, including avoidance of commercial influence.[75]

Appropriate suspicion of PH is the most important competency for generalist physicians. Confirmation of PH is relatively easy if one suspects PH. Generalist physicians must recognize exertional dyspnea and exercise limitation, including exertional syncope or presyncope, as cardinal symptoms (albeit nonspecific) of PH. They must include PH among the diagnostic possibilities when they diagnose common heart and lung disorders, such as asthma, and pursue the diagnosis of PH whenever diagnostic tests (eg, spirometry) or response to therapy are inconsistent with the initial diagnosis. They should have sufficient physical diagnostic skills to identify signs of PH, such as an abnormal right ventricular impulse, an increase in the intensity of the pulmonic component of the second heart sound, or the murmur of tricuspid regurgitation. They should understand the role of echocardiography as a screening test for PH and the role of cardiac catheterization as a diagnostic test. Whenever possible, they should have access to physicians with more advanced skills, especially cardiac and pulmonary imaging, pulmonary function testing, and cardiac catheterization.

General specialist physicians require more rigorous training. Skills relevant to the recognition, confirmation, differential diagnosis, and management of PH are essential competencies. Specialist physicians must understand basic and clinical aspects of PH. Table 2 identifies a number of core competencies for physicians who specialize in the diagnosis and treatment of cardiopulmonary diseases that include PH.

PH specialist physicians require the most rigorous training, a focused practice devoted to the diagnosis and treatment of PH, and advanced competency. Advanced skills relevant to the recognition, confirmation, differential diagnosis, and management of PH are essential competencies for PH specialists. PH specialists understand basic and clinical aspects of PH outlined in Table 2, and these physicians possess in-depth knowledge and experience (expert competency) such that they can serve as consultants for general specialist physicians (eg, cardiologists, pulmonologists, rheumatologists, or hepatologists). Table 3 identifies a number of core competencies for physicians who specialize in the diagnosis and treatment of PH (PH specialists).

Table 2—*Core Competencies for Physicians Specializing in the Diagnosis and Treatment of Cardiopulmonary Diseases That Include PH*

Basic physiology
Understand normal pulmonary vascular physiology
Understand pulmonary vascular pathophysiology
Understand normal right ventricular function
Understand acute and chronic right ventricular dysfunction
Understand the interactions and relationships between the right and left ventricles in normal physiology and in the setting of pulmonary vascular diseases
Understand the pathophysiology of congenital heart disease (eg, congenital systemic-to-pulmonary shunts)
Biology
Understand normal vascular biology (endothelium, smooth muscle)
Understand pulmonary vascular pathobiology
Genetics
Understand patterns of heritable PAH
Understand genetic tests relevant to heritable PAH
Pharmacology
Understand oxygen transport and use of supplemental oxygen
Understand diuretic management of right-sided heart failure
Understand warfarin pharmacology and toxicity
Know pharmacology and toxicities of endothelin receptor antagonists
Know pharmacology and toxicities of phosphodiesterase inhibitors
Know pharmacology and toxicities of prostacyclin analogs
Know drug-drug interactions between the various classes of PAH-specific therapies as well as between the conventional therapies (eg, ERAs-PDE 5 inhibitors, warfarin-ERAs)

ERA = endothelin receptor antagonists; PDE = phosphodiesterase. See Table 1 for expansion of other abbreviations.

How Can Worldwide Physician Education and Training in Pulmonary Hypertension Proceed?

There are a number of steps needed in order for worldwide education and training in PH to proceed. One step is an in-depth understanding of health-care systems, especially graduate and postgraduate medical education, in every country. The status of PH education in these systems also must be assessed. The PH community will need to identify educators and educational programs for generalists and general specialists. Additional PH specialist training programs will need to be developed. The PH community will also need to assist educators (eg, adult and pediatric cardiology, respiratory, and rheumatology training

Table 3—*Core Competencies for Physicians Specializing in the Diagnosis and Treatment of PH*

Diagnosis
Differentiate causes of PH reliably
Cardiac catheterization
Interpret hemodynamic measurements from right-sided heart catheterization
Assess measurements of cardiac output
Assess quality of hemodynamic pressure waveforms
Differentiate WHO diagnostic groups from hemodynamic data
Interpret oxygen saturation data from right-sided heart catheterization
Recognize left-to-right shunts and right-to-left shunts
Interpret acute vasodilator tests during right-sided heart catheterization
Define acute vasoreactivity
Imaging
Estimate right ventricular systolic pressure from echocardiography
Assess right ventricular function from echocardiography
Understand contrast echocardiography
Understand the use of transesophageal echocardiography in evaluation of PH
Differentiate acute from chronic thromboembolism
Differentiate operable from inoperable chronic thromboemboli
Identify radiographic pattern of pulmonary venoocclusive disease
Pharmacotherapy of PH
Identify expected response and toxicities of phosphodiesterase type 5 inhibitors
Identify expected response and toxicities of endothelin receptor antagonists
Titrate parenteral prostacyclin analogs and identify expected effects and toxicities
Understand management of patients with PH
Know effective contraceptive methods for PAH patients capable of childbearing
Know and have experience with perioperative management of patients with PH
Know criteria for lung or heart and lung transplantation for PH

WHO = World Health Organization. See Table 1 for expansion of other abbreviations.

program directors) in the development of curricula, educational materials, and examinations in order to create and assess competency. Further development of organizations whose mission includes global education and training in pulmonary vascular disease is another critical step. Ideally, these organizations will use the expertise of PH specialist physicians (eg, the Pulmonary Hypertension Association, the Pulmonary Vascular Research Institute), and integrate with societies that serve general specialist physicians (eg, American College of Chest Physicians, European Respiratory Society, American Thoracic Society, American Heart Association, European Society of Cardiology, International Society of Heart and Lung Transplantation, American College of Cardiology, Society for Pediatric Research), and generalist physicians (eg, American College of Physicians, American Academy of Pediatrics). General specialist societies already provide a variety of overlapping educational materials, including guideline statements (European Society of Cardiology, European Respiratory Society, International Society of Heart and Lung Transplantation,[76] American College of Cardiology/American Heart Association,[50] and the American College of Chest Physicians[49]), special symposia publications for the general specialist,[77] electronic education (Pulmonary Artery Catheter Education Project[78]; PHA online university[79]) and symposia and postgraduate courses at annual professional meetings.

Worldwide education and training in PH should integrate new technologies with traditional education and training procedures. The Internet provides global access to educational programs.[77] The Internet can support educational programs to regions of the world with limited resources. It can provide point-of-care access to information and protocols, and even telemedicine applications that allow generalist physicians to engage PH specialists halfway around the world.

Conclusions

Worldwide physician education and training have not kept pace with the advances in diagnosis, management, and understanding of PH. The development of curricula based on the needs of generalists, general specialists, and PH specialists is one essential step. Current educational technologies and strategies (eg, Internet education, educational symposia at medical society meetings, stand-alone meetings dedicated to PH education) as well as specific training efforts, such as regional PH task forces, can disseminate advances in the diagnosis and treatment of PH to underserved populations of the world in much the same way that dedicated physicians have achieved and sustained worldwide education in the diagnosis and treatment of TB during the past 40 years.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Elliott is an employee of Intermountain Healthcare, and Intermountain Healthcare has received support from Pfizer, Encysive, Actelion, Eli Lilly/ICOS, and United Therapeutics for contracts on which Dr Elliott is the site Principal Investigator. Dr Elliott serves as a consultant to Actelion as a member of the Steering Committee for the REVEAL registry. Intermountain Healthcare has filed a patent based on Dr Elliott's invention for the use of BMPR2 mutation analysis to assess vasoreactivity in pulmonary arterial hypertension. Dr Barst has received research grants and/or consultancy honoraria from Actelion, Eli Lilly, Pfizer, United Therapeutics, Novartis, Gilead, and GlaxoSmithKline. Dr Seeger received honoraria in 2006, 2007, and 2008 for speaking at a symposium organized by Bayer Schering Pharma AG, and in 2008 for speaking at a symposium organized by Lung Rx, Inc. He also received payment in 2009 for chairing a research workshop, and payment in 2008 and 2009 for chairing the PHUPDATE organized by Encysive. Dr Seeger received grant support from Lung Rx for a contract on which he is the site Principal Investigator, from Gilead in 2007/2008 for participating in a multicenter clinical trial, and from

Lung Rx in 2007/2009. He served as a consultant to Bayer Schering Pharma AG of the Steering Committee for the Ventavis Registry. Dr Zamanian is the recipient of an Entelligence/Actelion career development grant and is a consultant for Gilead and United Therapeutics Pharmaceuticals. Dr Rubin has received grant/research support from NHLBI, Actelion, Gilead, United Therapeutics, and Pfizer; serves or has served on advisory committees for Actelion, Pfizer, and Gilead; and serves or has served as a consultant for NHLBI, Actelion, Pfizer, United Therapeutics, Gilead, Aires Pharmaceuticals, Bayer Schering Pharma AG, MondoGEN, Solvay Pharmaceuticals, GeNO, BioMarin, Cytokinetics, CardioMems, Lexicon, and ErgoNex. He is also a stock shareholder for United Therapeutics and GeNO. Drs Porres-Aguilar and Brown report that no conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: We thank many colleagues around the world who have worked collegially to advance the understanding and care of those affected by PH. This work was performed at the Intermountain Medical Center and the University of Utah School of Medicine.

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