A Rare Opportunity in a Rare Disease

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Pulmonary hypertension (PH) is a chronic disease of the pulmonary vasculature, characterized by vessel remodeling that leads to increased pulmonary vascular resistance, right ventricular failure, and ultimately, death. While PH is somewhat simply defined as a mean pulmonary artery pressure (mPAP) on right heart catheterization (RHC) of greater than or equal to 25 mm Hg, the clinical, pathobiologic, and physiologic manifestations of the disease, and its subsequent impact on an individual patient, vary greatly. For example, while PH is defined by an elevated mPAP, current guidelines classify PH into 5 major categories, each with numerous subcategories based on clinical and physiologic features. Accordingly, proper classification of an individual patient requires an extensive evaluation that includes pulmonary function testing, submaximal exercise testing, several imaging studies, overnight oximetry, echocardiography, and ultimately, RHC. PH, regardless of etiology, imparts significant burden on patients, causing severe functional limitations and negatively impacting survival. Historically, in the era prior to the availability of specific pulmonary vasodilator therapies to treat patients with the rarest form of PH, pulmonary arterial hypertension, median survival was around 2 years. With the advent of targeted medical therapies over the past 30 years, the median survival has improved to more than 7 years. However, with these advances in therapies and the expanding availability of lung transplantation for most forms of PH, the complexity of care for patients with this disease has increased exponentially.

CLINICAL MANIFESTATIONS OF PH
The hallmark of pulmonary hypertension (PH) is breathlessness, typically with exertion, but progressing to dyspnea at rest in more severe states. Patients can experience fatigue, chest pains, and edema, among other symptoms. These symptoms are often attributed to other causes, leading to a delay in diagnosis of PH. Once properly diagnosed and classified, certain forms of PH, namely pulmonary arterial hypertension (PAH) and pulmonary hypertension in the setting of chronic thromboembolic disease (CTEPH), can be treated with pulmonary vasodilators or, in the case of CTEPH, pulmonary thromboendarterectomy. In either case, lifelong, burdensome therapies—often with significant side effects—are required to maintain health and improve outcomes. For example, patients with severe PAH are often placed on continuous infusions of intravenous prostacyclin therapy; these therapies require placement of an indwelling catheter through which medications are continuously infused via a portable pump. The patient is responsible for maintaining the access line and pump and preparation and administration of the medication on a daily basis. The side effects of such medications are often significant, including headaches, flushing, jaw and heel pain, chronic diarrhea, along with numerous others. Patients are also often on supplemental oxygen, which further adds to the disease burden and impairs quality of life. Such complex therapies are exceedingly expensive, often adding financial stress to patients and caregivers of those with this disease. These and other factors lead to impaired quality of life and contribute to a high prevalence of anxiety and depression in patients with this disease. Thus, PH in any form leads not only to significant hemodynamic and physiologic perturbations, but also to severe functional limitations and emotional burden.

THE CHALLENGE OF PH LEADS TO THE PULMONARY HYPERTENSION ASSOCIATION
The complexity of establishing the diagnosis and proper classification, selecting and initiating appropriate medical therapy, and delivering effective longitudinal care of patients with PH necessitates expertise in this disease state. However, given the rarity of certain forms of PH, namely PAH, and the potential deleterious effects of improper use of pulmonary vasodilator therapies in other forms of PH, expertise in the evaluation and management of PH is imperative. Both providers and patients have long recognized this need. Through a patient-initiated collaboration with experts in the care of patients with PH, the Pulmonary Hypertension Association (PHA), the largest patient advocacy group for patients with PH, was formed in 1991. This organization has been integral to raising awareness of PH in the community, including among providers. Educational programs for physicians and allied health providers, both through preceptorship conferences and online resources, have helped to disseminate guideline-recommended evaluation and management principles to providers.
in the community and to trainees in various disciplines. However, even with these laudable initiatives, active advocacy programs, and biennial international conferences for patients and providers, evidence accumulated that suggested significant delays in the diagnosis of PH and widespread nonadherence with guidelines for the evaluation and treatment of PH. For example, the mean time from symptom onset to diagnosis of PAH in the US-based REVEAL registry from 2012 was 33 months; in the National Institutes of Health registry from 1987, the average time to diagnosis was 24 months. These registry data suggest that no progress had been made in the timely diagnosis of PAH despite increasing awareness and availability of specific therapies for PAH. Further, in one observational study of both academic and community practices actively involved in the evaluation of patients with PH, researchers found that only 6% of patients who were given a diagnosis of PH had completed the entire guideline-recommended evaluation. These investigators also found frequent inappropriate use of medical therapy: for instance, only 7% of patients treated for PAH with calcium channel blockers had hemodynamic evidence of a positive vasodilator response, which is necessary to identify the subset of PAH patients who are likely to respond to calcium channel blocker therapy. These and other observations prompted the PHA and its scientific advisory arm, the Scientific Leadership Council (SLC), to consider the utility of establishing centers of excellence.

**THE CYSTIC FIBROSIS FOUNDATION CARE NETWORK AS A MODEL**

The motivation to pursue developing centers of excellence was largely based on the successes of the Cystic Fibrosis Foundation’s (CFF) Care Center Network. This network was established in 1960 by the CFF in recognition of the need to incorporate a multidisciplinary approach to the care of patients with a rare, fatal disease with multisystem involvement. The Center Committee, appointed by the CFF, generated criteria for care centers, focused on optimizing clinical care for patients and support for their families, developing research programs, and educating trainees to become the next generation of care providers and researchers. The criteria mandated that a center have a multidisciplinary team to address not only inpatient and outpatient medical care, but also psychological and sociological needs. In addition, the centers must abide by guideline-driven practices and maintain a sufficient number of patients in its practice to demonstrate adherence with these mandates. Initial accreditation requires a site visit with a detailed review of patient outcomes, program infrastructure, and program processes. Maintenance of status requires a site visit at least every 5 years with a similar review of clinical operations and infrastructure.

Initial accreditation was given to 2 centers, but the network rapidly expanded to more than 100 by 1980. While the network provided recognition of individual centers of excellence in clinical care and research, the advent of the CFF Patient Registry in 1966 proved to be an invaluable advancement. This registry, approved by the institutional review board, captures data from all centers in the Care Network as part of a longitudinal, observational study across the US. The registry has provided invaluable data on the natural history of cystic fibrosis (CF) and trends in treatment and complications. (Cystic Fibrosis Patient Registry. Cystic Fibrosis Foundation, Bethesda, MD 2017) Importantly, the registry has demonstrated remarkable trends in outcomes for CF over the past 25+ years: 1) improved median survival from less than 28 years to now over 41 years, and 2) evolving demographics from adults comprising less than 30% to now 50% of individuals with CF.

These data also offered opportunity to study outcomes at the individual center level. While initially controversial, these studies have provided important observations. Previously unrecognized variation in outcomes between centers allowed for comparisons between the best-performing centers and the remaining centers. Remarkable differences in survival, approaching 7 years, were noted between the top-performing centers and other centers in the network. Subsequent studies identified significant variability in adherence with treatment practice guidelines and hypothesized this variability contributed to the observed differences. The CFF recognized an opportunity to develop quality improvement initiatives across the Care Network. To this end, they promoted “benchmarking projects” to identify best practices in CF care. One of these early projects comparing 2 CF centers identified that high-fat as opposed to restricted-calorie diet was associated with improved nutritional outcomes and survival. Subsequent projects involved site visits by teams of physicians, allied health care providers, and CF parents with training in systems-oriented approaches to care. These teams were deployed to high-performing centers to better understand center-specific practice patterns, aspects that are not captured by data from the CFF Patient Registry that may impact patient care and outcomes. These visits identified 5 key features: systems, attitudes, practices, patient/family empowerment, and projects. These key practices have been subsequently assimilated into other centers’ practices under the guidance of the CFF.

Taken together, these examples highlight the impact the CFF Care Network and Patient Registry have had on patient care and offer strategies to best utilize data from both the registry and individual center practices. There are many similarities between CF and PH, particularly with PAH. Both are rare diseases that affect children and adults and are life-limiting. Both lead to significant physiologic impairment that cause dyspnea and functional limitations. Both require cumbersome therapies with a myriad of side effects that can negatively impact quality of life. Importantly, both require clinical expertise to properly diagnose and treat. The successes of this Care Network and Patient Registry served as strong support for the development of a similar program in PAH.

**CHALLENGES SPECIFIC TO PAH AND OTHER FORMS OF PH**

While there are numerous similarities between CF and PH, multiple distinct differences exist. Unique aspects
of PAH, including its epidemiology, clinical manifestations, diagnosis, and treatment, present challenges in the evaluation and management of this disease. Some of these also apply to other forms of PH, contributing to significant knowledge gaps in the proper clinical assessment of PH in general.

Recall recognition
As discussed above, despite increased awareness of PAH and availability of novel therapies to treat this disease, the average time to diagnosis of PAH from symptom onset is still nearly 3 years. This delay in diagnosis is potentially significant; although not definitively demonstrated in a randomized clinical trial, therapy earlier in the disease course may lead to improved outcomes. The reasons for delayed diagnosis included presence of concomitant diseases such as chronic obstructive pulmonary disease (COPD) and sleep apnea to which symptoms of dyspnea and fatigue were attributed. Importantly, screening recommendations exist only for patients with underlying risk factors for PAH, such as known or suspected heritable risk or underlying scleroderma. While screening for PAH in the general population is unlikely to be cost-effective or warranted, this differs significantly from CF where all 50 states in the United States have mandated newborn screening for the disease and thus offers the opportunity to identify disease early.

Diagnosis and Classification
Proper diagnosis and classification remains a significant issue in PAH and PH. As shown by McLaughlin and colleagues, only a minority of patients with a diagnosis of PAH have actually undergone a complete evaluation for PH in accordance with clinical practice guidelines. Nonadherence to these guidelines likely leads to misclassification of patients. As shown in the RePHerR Study, of 98 patients referred to a tertiary center for PH evaluation who were assigned a diagnosis prior to referral, 32 (33%) received a misdiagnosis based on subsequent evaluation and completion of the guideline-recommended evaluation. Other issues with proper diagnosis and classification may also exist, although the problems are less well quantified. For example, results from the study by McLaughlin and colleagues showed that less than 50% of PAH patients underwent ventilation-perfusion (V/Q) scans as part of their evaluation. V/Q scans are more sensitive than computed tomography angiograms in the detection of chronic pulmonary embolic disease. Since V/Q scans are a necessary test to exclude the possibility of CTEPH, it is likely that some patients diagnosed as PAH actually had CTEPH. Treatment approaches differ greatly for CTEPH vs. PAH; pulmonary thromboendarterectomy, if indicated, may be curative. Medical therapy differs as well; only the soluble guanylate cyclase stimulator riociguat is approved for this indication. Given the impact on prognosis and treatment modality, misclassification of PH remains an important issue.

Treatment
The study by Deano and colleagues also identified that over half of the patients who received PAH-specific therapy prior to referral to the tertiary center did not meet clinical criteria for PAH. Similar observations were recently reported in a large, population-based study in Canada. Using numerous administrative databases and verification of diagnosis of PH using chart review in a subset of patients, Wijeratne and colleagues found substantial use of PAH-specific therapies for patients with PH related to left heart disease and to lung disease. These data suggest that off-label use of PAH-specific therapies is common, adding significant cost burden to the health care system. In fact, inappropriate use of PAH therapies in patients with other forms of PH is one of 5 topics highlighted in the Choosing Wisely campaign by the American Board of Internal Medicine. This campaign (www.chosingwisely.org) is designed to address issues of overuse in medical evaluation and treatment. The fact that use of PAH therapy is one of the 5 most pressing problems in medicine emphasizes the significant knowledge gap that exists in the proper diagnosis and classification of PH.

This knowledge gap further extends to the appropriate referral of patients for advanced care. Deano and colleagues found that over 40% of patients with PH had World Health Organization functional class III or IV symptoms at the time of referral. In the REVEAL registry, Faber and colleagues found that only 56% of patients who died received advanced therapies with prostaclins in the months leading up to death. However, when compared to a high-volume center with clinical expertise in PAH, 70% of patients who died were receiving parenteral prostanoids at the time of death. This stark difference in use of advanced therapies could be explained by lack of expertise or availability of this therapy in certain practices.

Patient-Related Outcomes
PAH imparts a significant burden on patients and caregivers alike. Therapies are cumbersome and have profound side effects. Health-related quality of life (HRQOL) is impaired, frequently to the same extent as that seen in various cancers. Importantly, PAH-specific therapies may not significantly impact HRQOL as most studies have failed to demonstrate a clinically relevant improvement in HRQOL with initiation of PAH therapy. Similarly, dyspnea, the most common symptom in PAH, does not appear to improve with pulmonary vasodilators despite improvement in functional capacity and hemodynamics. Depression and anxiety are common and not often addressed by PH providers. Similarly, awareness of and referrals to palliative care are rare. Thus, current practice patterns may fail to address the most important symptoms or relieve disease burden for patients with PAH.

OPPORTUNITIES WITH THE PH CARE CENTER PROGRAM
In 2011, the SLC of the PHA recommended the PHA lead a program to develop a nationwide accreditation program for PH centers. The goals for the Pulmonary Hypertension Care Center (PHCC) program were the following: 1) increase disease awareness; 2) improve access to expert care; 3) raise the level of care at all centers through increased adherence to published guidelines and consensus statements; 4) provide a
CONCLUSION

There are numerous challenges in the diagnosis and management of PH. Establishment of a network of PHCCs will increase disease awareness in the community, provide a known referral center for evaluation of PH, and thereby potentially reduce the time to proper diagnosis and classification. The network will provide an opportunity for collaboration across centers to foster research initiatives. Importantly, the data obtained from the PHAR will allow for assessment of outcomes across the network and at the center level. This will lead to quality improvement initiatives that have the potential to set a new standard of care for patients with PH. For a rare disease such as PAH, the PHCC offers a rare opportunity.

References

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-D41.
2. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987;107(2):216-223.
3. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest. 2012;141(2):354-362.
4. Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry. Chest. 2011;140(1):19-26.
5. Taichman DB, Shin J, Hud L, et al. Health-related quality of life in patients with pulmonary arterial hypertension. Respir Res. 2005;6:92.
6. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related Quality of Life and Survival in Pulmonary Arterial Hypertension. Ann Am Thorac Soc. 2016;13(1):31-39.
7. Guillemin L, Armstrong I, Aldrichetti R, et al. Understanding the impact of pulmonary arterial hypertension on patients’ and carers’ lives. Eur Respir Rev. 2013;22(136):535-542.
8. McLaughlin VV, Langer A, Tan M, et al; Pulmonary Arterial Hypertension-Enhancement Research Initiative (PAH-QuERI) Investigators. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. Chest. 2013;143(2):324-332.
9. Chakinala MM, McLaughlin MD. Pulmonary Hypertension Care Centers. Adv Pulm Hypertens. 2014;12(4):175-179.
10. Quinton H. Using data to identify opportunities for change and to monitor progress. Pediatr Pulmonol. 2004;38:124S-125S.
11. Boyle MP, Sabadosa KA, Quinton HB, Marshall BC, Schechter MS. Key findings of the US Cystic Fibrosis Foundation’s clinical practice benchmarking project. BMJ Qual Saf. 2014;23 Suppl 1:i15-i22.
12. Corey M, McLaughlin FJ, Williams M, Levion H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol. 1988;41(6):583-591.
13. Galié N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet. 2008;371(9630):2093-2100.
14. Galié N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. Rev Esp Cardiol (Engl Ed). 2016;69(2):177.
15. Deano RC, Glasser-Kolm C, Rubenfire M, et al. Referral of patients with pulmonary hypertension diagnoses to tertiary pulmonary hypertension centers: the multicenter REPherral study. JAMA Intern Med. 2013;173(10):887-893.
16. Tuninari N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48(5):680-684.
17. Wijeratne DT, Lajkosz K, Brogly SB, et al. Increasing Incidence and Prevalence of World Health Organization Groups 1 to 4 Pulmonary Hypertension: A Population-Based Cohort Study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018;11(2):e003973.
18. Sikirica M, Iorga SR, Bancroft T, Potash J. The economic burden of pulmonary arterial hypertension (PAH) in the US on payers and patients. BMC Health Serv Res. 2014;14:676.
19. Farber HW, Miller DP, Melzter LA, McGoon MD. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. J Heart Lung Transplant. 2013;32(11):1114-1122.
20. Tonelli AR, Arelli V, Minai OA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2013;188(3):365-369.
21. Rivat G, Lacasse Y, Martin S, Bonnet S, Provencer S. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. Chest. 2014;146(3):686-708.
22. Khair RM, Nwaneri C, Damico RL, Kolb T, Hassoun PM, Mathai SC. The Minimal Disease in Pulmonary Hypertension: A Population-Based Cohort Study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018;11(2):e003973.