LESS IS MORE

Referral of Patients With Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers

The Multicenter RePHerral Study

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Importance: Pulmonary hypertension (PH) is a fatal disease. Although the prognosis of pulmonary arterial hypertension (PAH) has improved with targeted therapies, the outcome is dependent on early detection and an accurate diagnosis.

Objective: To determine the accuracy of PH diagnoses in patients referred to PH centers and the frequency of PAH-specific medication use despite an uncertain or incorrect diagnosis.

Design: Multicenter, descriptive, cross-sectional study. During a 10-month period in 2010 and 2011, data on newly referred patients were collected and entered into a secure Internet database.

Setting: Three large tertiary PH centers.

Participants: One hundred forty consecutive patients newly referred to PH centers were invited to participate, and all consented to do so.

Results: Of 140 patients referred with a mean age of 56 years, 95 (68%) were referred by cardiologists or pulmonologists and 86 (61%) had disease classified as World Health Organization functional class III or IV. Fifty-six of the prereferral diagnoses (40%) were PAH, 42 (30%) unknown, and 22 (16%) PH secondary to lung disease or hypoxia. Of the 98 patients who received a definitive diagnosis before referral, 32 (33%) received a misdiagnosis. Fifty-nine patients underwent catheterization of the right and/or left side of the heart for the first time at the tertiary center. Of the 38 patients who underwent catheterization of the right side alone, 14 (37%) received a different diagnosis after undergoing the procedure; of the 21 patients who underwent catheterization of both sides of the heart, 11 (52%) received a different diagnosis after undergoing the procedures. Forty-two patients (30%) had started receiving PAH-specific medications before referral, with 24 of the prescriptions (57%) contrary to published guidelines.

Conclusions and Relevance: Patients referred to PH centers for diagnosis and treatment are often referred late (with functional class III or IV disease), receive misdiagnoses, and are inappropriately prescribed medications. A reevaluation of educational efforts is required to improve awareness and the care and outcome of patients diagnosed as having PH.

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Of the 5 World Health Organization (WHO)-classified groups of pulmonary hypertension (PH), group 1 refers to pulmonary arterial hypertension (PAH), a rare disorder that is manifest by symptoms of progressive right-sided heart failure. It can be idiopathic, heritable, or associated with anorexigens or diseases such as systemic sclerosis, congenital heart disease, portal hypertension, and human immunodeficiency virus (HIV). Although the prognosis has improved with PAH-specific therapies, the outcome is dependent on early detection and an accurate diagnosis, particularly prior to reaching WHO functional class (FC) III or IV symptoms.[1-4] The pathogenesis, available treatments, and response to treatments differ among causes of PH. The other types of PH are pulmonary venous hypertension (PH due to left-sided heart disease or valvular disease; group 2), hypoxic and respiratory diseases (group 3),[3] chronic

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thromboembolic PH (group 4), and group 5 PH (miscellaneous diseases with varied pathophysiologic characteristics, eg, sarcoidosis, thyroid disorders, and end-stage renal disease necessitating hemodialysis).

Specific therapies for PAH such as prostacyclin analogues, endothelin receptor antagonists (ERA), and phosphodiesterase type 5 (PDE5) inhibitors are Food and Drug Administration approved and included in the evidence-based treatment algorithm for group 1 PAH.[5,6] Treatments for groups 2 through 5 are typically directed toward the underlying cause of the PH. However, there can be overlap between the various groups (eg, a patient with scleroderma-associated PAH who develops interstitial lung disease and/or left ventricular dysfunction), which can complicate the diagnostic approach, therapeutic choices, and anticipated outcomes.

Patients are often referred to PH centers with incomplete evaluations. The PH community is in the process of formally defining the term *PH center;* however, a center is typically characterized by the presence of PH-trained physicians and a PH-dedicated nursing team and is a participant in randomized controlled PH trials. Although it is reasonable to defer a full evaluation to a specialty center, it is concerning to PH specialists that patients are too often referred late in the course of their illness and administered PAH-specific medications without appropriate testing for monitoring of response and frequently without an accepted indication. In addition, these medications are expensive and difficult to manage, necessitating substantial safety precautions to prevent serious dosing mistakes and toxic effects (eg, liver failure, shock, and pulmonary edema). We designed and conducted this study to assess the accuracy of the diagnosis of PH in patients referred to PH centers and the appropriateness of use of PAH-specific medications based on current guidelines.

METHODS

A multicenter, descriptive, cross-sectional study was conducted in which information on consecutive patients newly referred to 3 tertiary PH centers (Baylor College of Medicine, University of Michigan, and University of Chicago) during a 10-month period in 2010 and 2011 was collected and entered into a secure Internet database. No patients declined to participate. We determined whether patients referred had an evaluation consistent with the published guidelines,[7,8] and we also evaluated the accuracy of diagnosis, appropriateness of treatment, and clinical status at referral according to FC I through IV. Tertiary centers that participated in the study of referral of patients with PH diagnoses to tertiary PH centers (RePHerral study) each had more than 10 years of experience treating PH. Each also had at least 2 PH-trained physicians and 2 PH-dedicated research nurses, and each had conducted more than 10 PH randomized controlled trials. This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review boards at each of the participating institutions approved the protocol, and written informed consent was obtained from all patients.

Published guidelines for evaluation and management of PH recommend an evaluation that includes an electrocardiogram; pulmonary function tests; ventilation-perfusion scan; high-resolution computed tomography of the chest; computed tomography with angiography of the chest; transthoracic echocardiogram with agitated saline to rule out the presence of a shunt; catheterization of the right side of the heart (RHC) (supplemented by catheterization of the left side of the heart [LHC] if a reliable wedge pressure cannot readily be obtained); laboratory tests including complete blood cell count, thyroid function test, HIV test, antinuclear antibody test, and liver function test; and an assessment of exercise capacity with a standardized 6-minute walk test (6MWT), a bicycle or treadmill exercise test, or cardiopulmonary exercise testing.[3,7,8]

All available medical records were reviewed prior to the initial consultation. The PH specialist performed additional or repeated tests if tests were of poor quality or lacked necessary values (eg, hemodynamic values at catheterization), prior echocardiographic images were not available for review, or the values obtained were internally inconsistent. On completion of consultation, the PH specialist determined whether the patient had PH and, if so, the diagnostic group and level of severity (based on FC, laboratory values, exercise testing, and physical examination). The specialist also chose the treatment. Within the database reporting, no distinction was made between prereferral and postreferral laboratory testing; this distinction was made for all other diagnostic tests.

Specific medications for PH, including ERA, PDE5 inhibitors, and prostacyclin, are recommended for group 1 PAH, with the choice dependent on the prognosis as estimated by means of clinical (eg, FC, B-type natriuretic peptide, and 6MWT) and hemodynamic parameters. We defined inappropriate use of PAH-specific medication as use in groups 2 and 3 or in patients ultimately found to have "no PH" after tertiary center evaluation based on available guidelines.[3,7,8] Inappropriate use was also defined as use of PDE5 inhibitors, ERA, or inhaled therapies in group 1 patients with FC IV symptoms. In contrast, although not completely adherent to guidelines, PH-specific treatment was considered appropriate in group 4 when pulmonary thromboendarterectomy was not indicated, and in preparation for or following pulmonary thromboendarterectomy with residual PH.[9] Duration of use of PAH-specific medications prior to referral was documented when available. Information was also gathered on the use of calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, and warfarin.

Descriptive analysis was performed with STATA, version 11 (StataCorp).

RESULTS

The 140 patients had a wide age range and were mostly women (**Table 1**). The most common diagnosis before referral was group 1 PH (56 patients [40%]), followed by "unknown" (42 patients [30%]). Forty-two patients (30%) started receiving PAH-specific therapies before referral (Table 1). Forty-four patients were receiving either a calcium channel blocker or angiotensin-converting enzyme inhibitor before referral (5 receiving both); none were prescribed these medications for PH treatment. Notably, more than half of participants (86 patients [62%]) were classified as having WHO FC III or IV disease at the time of tertiary center evaluation.

At the completion of the evaluation at the PH center (after referral), 72 patients (51%) had a change in diagnosis, with the most common final diagnoses being group 1 (58 patients [41%]), followed by no PH and groups 2 and 3 (29 patients [21%], 27 patients [19%], and 19 patients [14%], respectively). **Table 2** summarizes the prereferral and postreferral diagnoses by group. Of the 56 patients

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who initially had a diagnosis of group 1 PAH before referral, 41 (73%) were found to have group 1 PAH after referral and 7 (12%) did not have PH of any cause. Of the 42 patients initially carrying a diagnosis of unknown before referral, 14 (33%) were found to have no evidence of PH.

DIAGNOSTIC EVALUATION BEFORE REFERRAL AND AT THE TERTIARY CENTER

For laboratory testing, most patients underwent a complete blood cell count and liver and thyroid function tests (**Table 3**). All patients had a transthoracic echocardiogram as part of the workup (109 [78%] before referral); 99 patients (71%) had a pulmonary function test (72 [73%] before referral); and 84 patients (60%) had a measure of exercise capacity (17 [20%] before referral). More RHCs than LHCs were completed, with a relatively even distribution prereferral and postreferral between the tests. Fifty-nine patients underwent catheterization of the right and/or left side of the heart for the first time at the tertiary center. Of the 38 patients who underwent catheterization of the right side alone, 14 (37%) received a different diagnosis after undergoing the procedure; of the 21 patients who underwent catheterization of both sides of the heart, 11 (52%) received a different diagnosis after undergoing the procedures. Of the 106 patients who underwent diagnostic heart catheterizations either before referral or at the tertiary center, 14 of 100 had a mean pulmonary arterial pressure lower than 25 mm Hg, and 15 of 71 had a calculated pulmonary vascular resistance of less than 3 Wood units based on entered reliable data. These data mostly resulted in a diagnosis of no PH, with a few patients receiving a PH diagnosis at the discretion of the investigator (5 group 1 PAH, 2 group 2, and 3 group 3).

APPROPRIATENESS OF USE OF PH-SPECIFIC MEDICATIONS

Forty-two patients (30%) had started receiving PAH-specific medications before referral, with 11 receiving more than 1 therapy and most (41of 42 patients) receiving at least 1 oral therapy (**Table 4**). Only 23 of these patients received a diagnosis of group 1 PAH after tertiary center evaluation, and 1 of them received a diagnosis of inoperable group 4; therefore, 18 medication prescriptions (43%) were contrary to PH guidelines, most of them in group 3 patients. Also contrary to guidelines, 6 FC IV patients who were receiving oral PAH medications at the time of referral were ultimately determined to have group 1 PAH. Thus, 57% of the 42 patients receiving PAH medications at the time of referral had been prescribed them inappropriately. Furthermore, of the 42 patients referred with a PH diagnosis of unknown, 11 had started receiving PAH-specific therapy, and 5 patients had been prescribed a PH-specific medication without having undergone RHC (all PDE5 inhibitors).

GROUP 2 PH SECONDARY TO LEFT-SIDED HEART DISEASE SUBSET

Thirteen patients were sent to the tertiary centers with a group 2 PH diagnosis, of whom 6 had undergone LHC before referral. Of the 7 patients without LHC, only 2 remained as group 2 PH after evaluation at the tertiary center; 1 patient was found to have group 3 PH, and the others were found to have no PH.

Table 1. Characteristics of Patients Referred to Tertiary Pulmonary Hypertension Centers

Characteristic	Patients, No. (%)
Total[a]	140 (100)
Sex	
Female	98 (70)
Male	42 (30)
Site	
Baylor University	43 (31)
University of Chicago	67 (48)
University of Michigan	30 (21)
Referral source	
Physician	133 (95)
Self-referred	7 (5)
Referring physician	
Cardiologist	40 (30)
Primary care physician	10 (8)
Rheumatologist	15 (11)
Pulmonologist	55 (41)
Other/unknown	13 (10)
Referring location	
Academic university	38 (27)
Community hospital	19 (14)
Community physician's office	72 (51)
Unknown	11 (8)
WHO functional class	
I	15 (11)
II	37 (26)
III	71 (51)
IV	15 (11)
Unknown	2 (1)
Diagnosis at referral	
PAH – Group 1	56 (40)
PH – Left-sided heart disease – Group 2	13 (9)
PH – Lung disease – Group 3	22 (16)
PH – Chronic thromboembolic – Group 4	4 (3)
PH – Group 5	2 (1)
PH – Unknown	42 (30)
No PH	1 (1)
PH-specific medications at referral	
Prostacyclin	4 (3)
ERA	17 (12)
PDE5 inhibitor	33 (23)
Combination	11 (26)
Other medications at referral	
CCB	30 (21)
ACE inhibitor	19 (14)
Diuretics	52 (37)
Warfarin	23 (16)
Supplemental oxygen	38 (27)
CPAP/BiPAP	18 (13)
Receiving PH medications without RHC	
No	135 (96)
Yes	5 (4)

Abbreviations: ACE, angiotensin-converting enzyme; BiPAP, bilevel positive airway pressure; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension; RHC, catheterization of the right side of the heart; WHO, World Health Organization.

[a] Mean age (range), 56 (18-92) years.

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Table 2. Prereferral Diagnosis Compared With Postreferral Diagnosis[a]

	Postreferral Diagnoses, No. (%)						
Prereferral diagnosis	Group 1 (n = 58)	Group 2 (n = 27)	Group 3 (n = 19)	Group 4 (n = 3)	Group 5 (n = 1)	No PH (n = 29)	Unknown (n = 3)
Group 1 (n = 56)	**41 (73)**	3 (5)	4 (7)	0	0	7 (12)	1 (2)
Group 2 (n = 13)	0	**8 (62)**	1 (8)	0	0	4 (31)	0
Group 3 (n = 22)	4 (18)	3 (14)	**13 (59)**	0	0	2 (9)	0
Group 4 (n = 4)	0	0	0	**3 (75)**	0	1 (25)	0
Group 5 (n = 2)	0	0	0	0	**1 (50)**	1 (50)	0
No PH (n = 1)	1 (100)	0	0	0	0	**0**	0
Unknown (n = 42)	12 (29)	13 (31)	1 (2)	0	0	14 (33)	**2 (5)**

Abbreviation: PH, pulmonary hypertension.
[a]Totals may not equal 100% due to rounding. Boldface indicates patients who remained in the same diagnosis group after reevaluation at the PH center. Group 1, pulmonary arterial hypertension; group 2, PH left-sided heart disease; group 3, PH lung disease; group 4, chronic thromboembolic PH; group 5, miscellaneous PH.

Table 3. Pulmonary Hypertension Evaluation

	Patients Tested, No. (N = 140)		
Test	Prereferral	At Tertiary Center	Total Tested, No. (% of Total Cohort [N = 140])
CBC	NR[a]	NR[a]	125 (89)
HIV	NR[a]	NR[a]	40 (29)
ANA	NR[a]	NR[a]	69 (49)
TFT	NR[a]	NR[a]	97 (69)
LFT	NR[a]	NR[a]	120 (86)
TTE	109	31	140 (100)
PFT	72	27	99 (71)
V/Q scan	33	39	72 (51)
HRCT of chest	49	27	76 (54)
CTA	23	12	35 (25)
RHC	47	59	106 (76)
LHC/angiogram	36	21	57 (41)
TMT	2	23	25 (18)
6MWT	15	44	59 (42)

Abbreviations: 6MWT, 6-minute walk test; ANA, anti–nuclear antibody test; CBC, complete blood cell count; CTA, computed tomography angiography; HIV, human immunodeficiency virus; HRCT, high-resolution computed tomography; LFT, liver function test; LHC, catheterization of the left side of the heart; NR, not recorded; PFT, pulmonary function test; RHC, catheterization of the right side of the heart; TFT, thyroid function test; TMT, treadmill test; TTE, transthoracic echocardiogram; V/Q, ventilation-perfusion.
[a]The study database did not differentiate whether laboratory tests were performed before referral or by the PH center. This distinction was made for all other testing.

COMMENT

In spite of major efforts to educate medical professionals about PH, our study demonstrates that patients diagnosed as having PH often receive misdiagnoses and are prescribed PAH-specific medications contrary to guidelines. To our knowledge, this is the first study designed specifically to assess the accuracy of diagnosis and the frequency of inappropriate prescriptions in patients referred to tertiary PH centers. Not only did one-third of all patients have an incorrect prereferral diagnosis, more than half had FC III and IV disease, and 57% had been prescribed PAH-specific medications (PDE5 inhibitors, ERA, or prostacyclin) contrary to PH guidelines. After referral to a tertiary center, 40 of 42 patients (95%) previously not given a definitive diagnosis finally received one, often something other than PH. Given the rarity of PAH, it is understandable that many physicians may have deferred a complete evaluation to a specialized center, illustrating the value of this team approach from a patient, physician, and cost perspective.

A concerning number of patients had not undergone RHC, a test required by the European and American cardiology and pulmonary societies to confirm the presence of PAH, to help predict prognosis, or to provide a baseline measurement of hemodynamics for therapeutic monitoring.[7,8] It appears that the diagnosis was determined primarily by means of transthoracic echocardiogram, which is a good screening test but can be inaccurate, with underestimation or overestimation of the actual mean pulmonary arterial pressure.[7,10,11] Many patients received an incorrect diagnosis when RHC and LHC were not performed before referral. Because we could not blindly review prereferral RHC and LHC studies for accuracy, we cannot identify whether the incorrect diagnoses were related to the quality (eg, poor pressure readings), completeness, or interpretation of these tests. When the PH center completed these tests, the diagnosis changed, illustrating their critical diagnostic importance.

Specific medications for PAH have potential toxic effects (liver failure, shock, and pulmonary edema), can be cumbersome to administer, and are expensive, but they can improve mortality rates and functional status if used appropriately in patients with PAH.[7,8] The use of PDE5 inhibitors in patients with group 2 PH might be effective,[12-15] but its role in general usage or in those with heart failure and preserved ejection fraction is unclear.[16] Recent data seem promising, showing improvements in pulmonary pressure, right ventricular function, left ventricular relaxation and distensibility, and lung interstitial water metabolism (by decreasing wedge and right atrial pressure).[17] Further investigation by the Heart Failure Clinical Research Network's Phosphodiesterase-5 Inhibition to Improve Quality of Life and Exercise Capacity in Diastolic Heart Failure (RELAX) trial (clinicaltrials.gov Identifier: NCT00763867) is ongoing. On the basis of existing evidence, this strategy should not be considered standard clinical practice, since benefits do not out-

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Table 4. Patients Receiving PAH-Specific Medications Prior to Referral Stratified by Postreferral Diagnosis

	Postreferral Diagnoses, No.[a]				
Medication	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**No PH**
Prostacyclin	0	1	0	0	0
ERA	4	2	1	0	0
PDE5 inhibitor	10	3	6	1	3
PGI2/ERA	0	0	1	0	0
PGI2/PDE5 inhibitor	1	0	0	0	0
ERA/PDE5 inhibitor	7	0	1	0	0
PGI2/ERA/PDE5 inhibitor	1	0	0	0	0
Total	**23**	**6**	**9**	**1**	**3**

Abbreviations: ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension.
[a] Group 1, pulmonary arterial hypertension; group 2, PH left-sided heart disease; group 3, PH lung disease; group 4, chronic thromboembolic PH; group 5, miscellaneous PH.

weigh risks. Studies of the use of both nonselective and selective ERA in patients with group 2 PH have displayed short-term hemodynamic improvement[18,19] but no long-term outcome benefit[20-23] and at considerable risk: the adverse event profile includes elevated levels of liver enzymes and increased fluid retention.[19,20,24,25]

In the RePHerral study, more than half of the time that medications were initiated contrary to guidelines, they had been prescribed to patients with group 3 PH, despite little existing evidence of benefit and data indicating potential detriment. A survey of 453 physicians, 94% of them pulmonologists, found that approximately 30% of physicians did not perform RHC to confirm the diagnosis of PH prior to initiating PH-specific therapy in patients with lung disease. Nearly all of the respondents believed that current PH-specific treatments were effective in this population, and many prescribed bosentan (nonselective ERA) or sildenafil (PDE5 inhibitor).[26] Data contrary to this belief, published shortly thereafter, were the findings of the unsuccessful multicenter, double-blind, randomized, placebo-controlled trial of sildenafil in patients with advanced idiopathic pulmonary fibrosis.[27] Patients did not show improvement in 6MWT distance and had only marginal improvement of arterial oxygenation, dyspnea, and quality of life. This lack of improvement seemed unrelated to the risk of worsening hypoxemia secondary to worsening gas exchange. In addition, a study of ambrisentan (type A selective ERA) in pulmonary fibrosis with or without PH showed that the drug lacked efficacy, and the cumulative data promoted the addition of idiopathic pulmonary fibrosis as a contraindication in the prescribing information.[28]

Delayed referral to PH centers is a continuing problem despite educational initiatives. Many patients who were referred late and who required parenteral prostacyclin might have been candidates for oral medication and oral combination medication if referred earlier in their course.[2,29] It appears that there may be an increase in clinicians' confidence in their ability to treat patients with PH, which results in a delay in referral to tertiary PH centers,[5] often without the correct diagnosis, as demonstrated by our study. Patients with advanced disease may not be responsive to therapies, including prostacyclin, or may no longer be lung transplant candidates.[29] Advanced FC (FC III or IV) is a known poor prognostic indicator,[30-32] and we found that more than 60% of the referred RePHerral participants had disease this advanced. Even if the medications are appropriately administered, delayed referral translates into a higher rate of severe clinical and hemodynamic instability.[33] Equally concerning was the number of referrals among patients with disease classified as FC IV who were receiving oral PAH medication. Not only were patients with FC IV PAH only receiving oral therapy (mono or dual), but also many receiving PAH-specific medications did not have PAH at all. Survival of PAH seems to have considerably improved at PH referral centers,[30-32,34-36] advocating for earlier referral. Furthermore, because the treatment of PAH necessitates a complex strategy that may involve multiple therapies and may require repeated hemodynamic testing to monitor progression, patients for whom therapy is being considered would likely benefit from referral to a tertiary PAH center.[4,7]

The main limitation of our study is that it is a cross-sectional study and did not use any longitudinal data to track outcomes. In addition, because referral sites did not follow a specific diagnostic algorithm, we were unable to determine whether tests had been performed appropriately and were helpful in making the correct diagnosis. For example, a negative result on a ventilation-perfusion scan is helpful in ruling out thromboembolic disease, but if the patient had a no PH diagnosis before referral and later received a diagnosis of PAH, the negative ventilation-perfusion scan result did not help contribute to the final misclassification. Another limitation is that the postreferral diagnosis was obtained after the first visit to the tertiary PH, often using studies performed outside the PH center and thus potentially subject to operator error. We were unable to determine the numbers of repeated heart catheterizations because our database entry forms were not designed to capture this information. We know that that this occurred but cannot confidently report frequency. The limitations of our database did not allow us to determine whether patients had been classified as FC IV for more than 3 months prior to referral or experienced a decline in FC and were not referred for an extended period. In addition, medications may have been initiated immediately prior to referral with the intention of allowing the PH specialist to decide whether the patient required it. These factors should be captured in future analyses.

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In conclusion, patients referred to PH centers for diagnosis and treatment are referred with advanced disease and are often misdiagnosed, misclassified, and treated inappropriately with PAH medications or undertreated in cases of severe PAH disease. Although it is understandable that patients are often referred without a complete evaluation, we caution against inexperienced clinicians offering a patient a definitive diagnosis that implies a poor prognosis. As emphasized in the guidelines, physicians should refer patients early in the diagnostic process to PH centers prior to medication initiation, even if the prereferral diagnosis is incomplete. Physicians with experience in the technical and interpretive aspects of PH should perform RHC with vasodilatory testing prior to administration of medication. Optimally, patients with a diagnosis of PAH should be referred to PH centers for confirmation and joint management so as to provide experienced care including earlier initiation of advanced therapies, potential enrollment in studies of novel or approved therapies, and consideration for transplant listing. The success of this approach also requires that the PH referral center respond to and communicate with the referring physicians and their patients. It seems that current educational efforts have not succeeded in promoting early diagnosis, early referral, or the importance of the diagnostic and treatment algorithm, necessitating a reevaluation of approaches to improve the care of patients with PH.

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EDITOR'S NOTE

Improving Care for Patients With Pulmonary Hypertension

Pulmonary hypertension is a life-threatening condition. Effective treatments are available for some types of pulmonary hypertension, but Deaño et al find that half of patients referred to pulmonary hypertension centers are referred late in the course, when treatment is unlikely to be effective. In addition, more than half of patients who had started receiving medications did not have the type of pulmonary hypertension that would be expected to respond to these medications. As these drugs have definite harms (liver failure, shock, edema) and no known benefit outside of group 1 pulmonary hypertension, we consider this a Less Is More article.

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