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Management of adult patients with PAH in Spain: current practice, resources, and needs (AIRE17 Study)

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ABSTRACT

Introduction and objectives: The objective of this study was to analyze, based on the opinion of healthcare professionals, human and material resources dedicated to the clinical management of patients with pulmonary arterial hypertension (PAH) as well as the needs and areas for improvement in the care of these patients in Spain.

Methods: A cross-sectional and multicenter study based on a survey was designed. Participants were physicians involved in the management of PAH. They completed an *ad hoc* 28-item questionnaire.

Results: Twenty specialists completed the questionnaire (45% pulmonologists, 35% cardiologists 15% specialists in internal medicine, and 5% pediatric cardiologists), 75% of whom developed their professional activity in a pulmonary hypertension unit pulmonary hypertension (PH), with a median experience of 11.5 years. A total of 75% manifested that a unit of PH was available at the hospital, with a mean number of 19.8+/- 42.0 new patients seen in 2015 (mean +/- SD). Ninety percent of participants reported the possibility to facilitate access to genetic counseling for their PAH patients. Adherence to the current guidelines of the European Society of Cardiology/European Respiratory Society (ESC/ERS), specifically regarding the diagnosis of PAH, was 90%. Three areas for improvement were identified by 2/3rd of respondents: the availability of technical and human resources, continuing education and access barriers to drug prescription.

Conclusions: PAH management in Spain is mainly undertaken by PH hospital units, where healthcare is provided in accordance with the current standards. Structural deficiencies have

Abbreviations: ESC, European Society of Cardiology; ERS, European Respiratory Society; PAH, pulmonary arterial hypertension; REHAP, Pulmonary Arterial Hypertension Spanish Registry.

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been identified in this analysis, which should be actively addressed in future improvement strategies.

Manejo de pacientes adultos con HAP en España: práctica actual, recursos y necesidades (Estudio AIRE17)

Palabras clave:
Hipertensión arterial pulmonar
Estudio transversal
Encuesta
Recurso asistencial
Necesidad asistencial

RESUMEN

Introducción y objetivos: El objetivo del estudio fue analizar las unidades dedicadas al manejo clínico de los pacientes con hipertensión arterial pulmonar (HAP) y las necesidades y puntos de mejora en la atención de los pacientes en España.

Métodos: Se diseñó un estudio multicéntrico y transversal basado en una encuesta. Los participantes fueron médicos involucrados en el manejo de la HAP. Completaron un cuestionario *ad hoc* de 28 ítems.

Resultados: Un total de 20 especialistas completaron la encuesta (45% neumólogos, 35% cardiólogos, 15% especialistas en medicina interna y 5% cardiólogos pediátricos), de los cuales un 75% trabajaba en una unidad de hipertensión pulmonar (HP), con una mediana de experiencia profesional de 11,5 años. Un 75% manifestó que su hospital disponía de unidad de HP, con una media ± desviación estándar de nuevos pacientes atendidos en el 2015 de 19,8 (42,0). En un 90% de los centros se disponía de la posibilidad de ofrecer consejo genético a los pacientes. La adherencia a las guías de la *European Society of Cardiology/European Respiratory Society* (ESC/ERS), especialmente en el diagnóstico de la HAP fue del 90%. Tres áreas de mejora fueron identificadas por 2/3 de los encuestados: la disponibilidad de recursos técnicos y humanos, el acceso a la formación continuada y la eliminación de barreras a la libre prescripción.

Conclusiones: El manejo de la HAP en España se lleva principalmente a cabo por las unidades hospitalarias de HP, siguiendo los estándares actuales. En este análisis se han detectado deficiencias estructurales que deberían abordarse activamente en futuras estrategias de mejora.

Introduction

Pulmonary arterial hypertension (PAH) is a severe cardiopulmonary disease,[1,2] with estimates of incidence in adults of 5–10 subjects per million/year and 15–60 adult subjects per million.[3] In population-based registries of PAH, incidence and prevalence rates range between 2.0 and 7.6, and 5.9 and 26 subjects per million of the population/year, respectively.[4,5] Despite advances in the treatment of PAH,[6–10] there is still a substantial proportion of misdiagnosed patients and inappropriate treatment of PAH in clinical practice.[11–13] Although consensus documents and clinical practice guidelines for the diagnosis and treatment of pulmonary hypertension have been published,[3,7,14,15] different studies have confirmed the lack of consistency between recommendations and clinical practice.[12,16,17]

It is estimated that there are 30–35 active PAH units in Spain (data from the REHAP registry).[18] At national level, there is a great variability regarding the organizational models for the care of PAH patients. The knowledge of the characteristics and resources available in the units involved in the healthcare of PAH patients is important as a starting point to design strategies for improvement. The primary objective of the study was to analyze the units dedicated to the clinical management of patients with PAH, the available resources, and the characteristics of current clinical practice in the management of PAH, as well as to identify the needs and areas of improvement in the care of these patients in Spain. Secondary objectives were to collect information on the structure of PAH units, to determine the clinical profile of patients seen in these units, and to evaluate the knowledge and level of adherence to the current guidelines for the management of patients with PAH.

Methods

A cross-sectional and multicenter study based on a survey was designed for the collection of data.

The questionnaire was developed by a scientific board composed of a cardiologist and a pulmonologist, with considerable experience in the care of patients with PAH. The questionnaire consisted of 28 items, grouped into four main sections: (a) structure of the pulmonary hypertension unit (11 items and

9 subitems); (b) care of the patient with PAH (7 items and 4 subitems); (c) available resources and care requirements for PAH adult patients (6 items); and (d) adherence to current clinical practice guidelines (4 items and 2 subitems).

Participants in the study were mainly cardiologists and pulmonologists along with other specialists working in Spanish hospitals involved in the care of adult patients with PAH.

The fieldwork was carried out from January 30th to July 1st, 2017. The participants were mostly recruited among members of the Pulmonary Arterial Hypertension Spanish Registry (REHAP)[18] through invitations sent by e-mail. Also, cardiologists and pulmonologists who met the inclusion criteria, registered in the Medynet database (a website platform for healthcare professionals), were invited to participate in the study. Physicians who, after receiving information of the study, accepted to participate were provided with the microsite URL where the questionnaire was lodged and the user's password. Participation in the study was anonymous, voluntary, and unpaid.

Descriptive statistics included frequencies and percentages for categorical variables and mean ± standard deviation for continuous variables. Data were analyzed using the SAS statistical program (Statistical Analysis Systems, SAS Institute, Cary, NC, United States) version 9.1.3 for Windows.

Results

Participants

A total of 20 specialists participated in the study (45% pulmonologists, 35% cardiologists, 15% specialists in internal medicine, 5% pediatric cardiologists). The study sample was representative as included more than 50% of PAH units of the country. Seventy-five percent of participants developed their professional activity in PAH unit. The professional description of participants and etiology of PAH usually seen in clinical practice are shown in Table 1.

Table 1 – Characteristics of participants in the study.

Variable	Number (%)
Total participants	20 (100)
Service in which professional activity is developed	
Cardiology	7 (35.0)
Pneumology	9 (45.0)
Internal medicine	3 (15.0)
Other (pediatric cardiology)	1 (5.0)
Professional activity in pulmonary hypertension unit	
Yes	15 (75.0)
No	5 (25.0)
Years of professional activity in the care of PAH	11.9 ± 5.0
Number of patients seen each year	39.5 ± 31.5
Etiology of PAH usually seen in clinical practice	
Idiopathic and/or familial	23.1 ± 18.0
Chronic thromboembolic pulmonary hypertension	24.6 ± 21.0
Pulmonary hypertension associated with connective tissue disease	18.7 ± 14.8
Pulmonary hypertension associated with congenital heart disease	14.6 ± 14.3
Portopulmonar hypertension	4.7 ± 5.7
Hypertension associated with HIV	4.0 ± 6.0
Hypertension associated with toxics or drugs	2.5 ± 2.9
Veno-occlusive pulmonary hypertension or pulmonary capillary hemangiomatosis	0.9 ± 1.6
Other types of PAH	6.8 ± 10.5

PAH, pulmonary artery hypertension.
Data are expressed as no. (%) or mean ± standard deviation.

Structure of the pulmonary hypertension units

We did not divide the quantitative analysis into two categories (local PAH units and expert PAH units), due to the small N of the study sample.

In the centers in which a unit of pulmonary hypertension was available, it depended on the service of pneumology in 73% of cases, or both the services of pneumology and cardiology in 33.3%. Pulmonary hypertension units were recognized as national reference center in 13% of cases. The mean number of patients with PAH currently managed in the unit was 78.3 ± 96.3, with a mean of new patients in 2015 of 19.8 ± 42.0 and a mean number of follow up consultations of 102.1 ± 131.2. In 90% of the cases, PAH units have a dedicated space available for consultations, hospitalization beds in 50% (mean 12.5 ± 12.4 beds), and intensive care unit beds in 50% (mean 5.5 ± 3.8 beds).

The mean number of professionals who participated in the PAH units varied from 1.3 for internal medicine specialists to 2.2 for pulmonologists and 2.8 for cardiologists. In 73.5% of the cases, the PAH unit was involved in residency training programs. Multidisciplinary specific sessions were established in 60% of the cases (11% weekly and 66.7% in a monthly basis). The cross-functional collaborative relationship with other services for the management of PAH patients is shown in Table 2.

On the other hand, 75% of the centers participated in PAH registries (86.7% of them at national level). Regarding research activities, 40% of the units participated in research protocols designed at the hospital and 65% in protocols designed by third parties. The mean number of research projects in which the respondents had participated in the last 5 years was of 3.5 ± 5.4.

Healthcare provided to pulmonary artery hypertension patients

Eighty percent of participants indicated that their unit received adult patients with PAH referred from other areas within the hospital. Also, 90% of the surveyed physicians referred patients to other PAH units.

According to 35% of the participating physicians, less than 25% of patients with PAH received specific health education and according to another 35%, this percentage was higher than 76%. Surveys to assess the patient's quality of life were performed only by 15% of the respondent physicians, and less

Table 2 – Relationship with other services and availability in the hospital of collaborative and/or complementary services.

Resource	Percentage of responses		
	No	Yes, at the participant's hospital	Yes, by agreement with another center
Do you have regular relationship with the following services, important for certain specific subgroups of pulmonary hypertension?			
Rheumatology (in case of not having a member integrated in the unit)	5	95	
Digestive system/hepatology	5	95	
Pediatric cardiology	40	55	5
Adult congenital cardiopathies	15	55	30
Abroad reference center in pulmonary hypertension	85	10	5
Unit of Infectious diseases/follow-up of patients with HIV	10	90	
Does the center have the following collaborative/complementary services for the care of patients with pulmonary hypertension?			
Hemodynamic-Cardiology Interventional unit	5	80	15
Service of Thoracic Surgery	15	55	30
Service of Cardiac Surgery	15	50	35
Service of Vascular Surgery/Radiology	5	80	15

HIV, human immunodeficiency virus.

than 40% of them have the support of social workers and/or psychologists on a routine basis. Finally, 90% of the participants reported availability of genetic counseling either in their own PAH unit (20%) or by agreement with other centers (70%).

Available resources and healthcare needs of the adult pulmonary artery hypertension patient

Almost all diagnostic resources were available at the centers of the surveyed physicians (Table 3). However, cardiac magnetic resonance imaging was not available in 10% of the units, diffusing capacity of the lungs for carbon monoxide test in 5%, ventilation/perfusion scintigraphy in 65%, and ergospirometry test in 5%. Moreover, 10% of units did not have access to genetic studies. Eighty percent of participants reported that pulmonary vasodilation testing was available in their own center (epoprostenol was the most commonly used drug) and 60% had access to pulmonary angiography. Pharmacological, interventional, and surgical resources are shown in Table 4.

According to the opinion of 70% of the surveyed physicians, less than 25% of patients required being hospitalized due to PAH clinical worsening. The 85% of respondent physicians reported that the mean duration of hospitalizations was between 5 and 10 days.

More than 60% of participants identified access to technical and human resources and to continuing education, jointly with the elimination of administrative barriers to drug prescription, as areas for improvement. The results are shown in Fig. 1.

Adherence to clinical practice guidelines

All participants reported adherence to the European Society of Cardiology (ESC) and European Respiratory Society (ERS) (ESC/ERS) guidelines for the diagnosis of the disease. Also, 90% recognized the implementation of mentioned guidelines in the treatment of PAH, whereas the remaining 10% did not used ESC/ERC guidelines because of the existence of a protocol specific to the hospital, restrictive in terms of treatment. At the time of selecting treatment for a patient recently diagnosed with PAH, PAH prognostic/risk factors were taken into consideration by all respondents, including clinical signs of heart failure (100%), hemodynamic parameters (100%) or plasma level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (90%). Cardiopulmonary exercise testing (whose implementation is not mandatory but recommended by the ESC/ERS Guidelines), was the least used prognostic factor, reported by 70% of participants. Finally, 90% of physicians considered that the standard timing for follow up assessments was every 3–6 months.

Discussion

The professional profile of physicians who participated in the study supports the relevance of the data obtained. Taking into account that the REHAP registry (Spanish Registry of Patients with Pulmonary Artery Hypertension) involves the participation of 38 hospitals, the sample size of this survey would cover more than 50% of the PAH units in the country. A high percentage of participants had an experience of more than 11 years and treated a considerable number of PAH patients annually, were chiefs of service, leaders or coordinators of a PH unit and were contributing members of the REHAP Spanish registry of Pulmonary Hypertension.[18]

On the other hand, in a multinational study with a similar design, assessing the extent to which PAH experts shared common practice patterns in alignment with published recommendations,[13] survey respondents were from 25 countries and 6 continents. The study concluded that in general practice patterns among PAH experts diverge from consensus recommendations, suggesting that opportunity may exist to improve care quality.

Conversely, the results obtained in the present study suggest that a vast majority of PAH units members of the REHAP group that participated in this survey, adhere the ESC/ERS guidelines of pulmonary hypertension in clinical practice, although some opportunities for improvement were also identified.

Regarding the structure of the units for the management of patients with PAH, 75% of the respondents' hospitals had

Table 3 – Diagnostic resources available at the hospitals of the 20 physicians surveyed.

Resource	Percentage of responses		
	No	Yes, at the participant's hospital	Yes, by agreement with another center
General laboratory tests		100	
Blood gases		100	
Microbiology laboratory		100	
Immunology laboratory		100	
Thrombophilia study		100	
Genetics of pulmonary hypertension	10	20	70
Electrocardiogram		100	
Chest X-rays		100	
Transthoracic echocardiography		100	
Transesophagic echocardiography		100	
Cardiac magnetic resonance imaging	5	80	15
Spirometry		100	
Respiratory function test with DLCO	5	90	5
Ventilation/perfusion scintigraphy		35	65
High-resolution CT scan		95	5
Angio-CT of pulmonary arteries		100	
Abdominal ultrasound		100	
6-minute walk test		100	
Ergospirometry	5	80	15
Right heart catheterization		85	15
Pulmonary vasodilator challenge	5	80	15
Epoprostenol	25	65	10
Adenosine	60	30	10
Nitric oxide	45	45	10
Sildenafil	10	45	45
Other drugs		100	
Selective pulmonary angiography	15	60	25

DLCO: carbon monoxide diffusing capacity; CT: computed tomography.

Table 4 – Therapeutic resources available at the hospitals of the 20 physicians surveyed.

Resource	Percentage of responses		
	No	Yes, at the participant's hospital	Yes, by agreement with another center
Oral medication			
Sildenafil		100	
Tadalafil	25	75	
Bosentan		100	
Ambrisentan	5	95	
Macitentan	25	75	
Riociguat	10	90	
Selexipag	75	25	
Inhaled medication			
Iloprost	5	90	5
Treprostinil	80	15	5
Subcutaneous medication			
Treprostinil	45	45	10
Intravenous medication			
Epoprostenol	25	70	5
Epoprostenol thermostable formulation	40	55	5
Treprostinil	85	15	
Sildenafil	55	45	
Other therapeutic resources			
Atrial septostostomy	55	25	20
Pulmonary angioplasty	50	10	40
Pulmonary thromboendarterectomy	35	5	60
Lung transplantation	35	15	50
Heart-lung transplantation	50	10	40

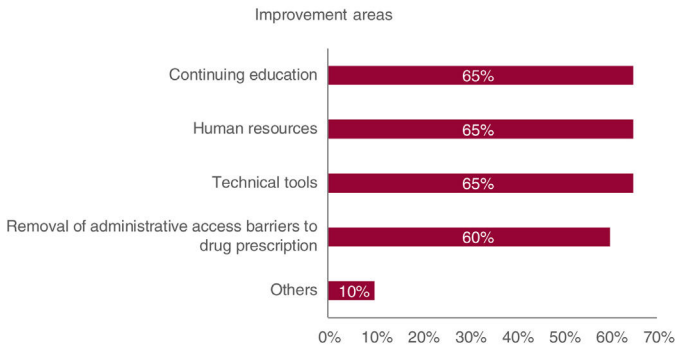

Fig. 1 – Improvement areas highlighted by specialists.

a PAH unit, however their role as a reference center was limited. Although not all PH units have hospital beds available for PAH patients, critical care units were available in 50% of the centers for the more severe patients. Another aspect to be highlighted is that only 60% of PAH units held specific multidisciplinary meetings, mostly on a monthly basis. Given the complexity of the management of patients with PAH, it seems reasonable to improve this aspect. In fact, an adequate diagnosis and the multifactorial approach to assess the prognosis of the disease in individual subjects are key aspects in the care of patients with PAH and require experience, technical training and multidisciplinary care to achieve optimal outcomes.[19,20]

Although 75% of units participated in registries of pulmonary hypertension, mainly at national level, the research activity was scarce with a median participation in collaborative research projects in the last 5 years of only 1.5 [range 1–25]. It is necessary to implement strategies and to provide resources aiming to increase the scientific research capacity of PAH units and to enhance the visibility and impact of these activities at national and international levels.

More than half of the respondents treated patients in functional class III/IV, which indicates the severity of the disease and the marked limitation of physical activity of these patients. The survey has revealed some aspects that deserve attention, such as the variable percentage of patients with PAH who receive health education, the scant attention paid to quality of life assessments, and the frequent lack of access to support from social workers or psychologists'. Several studies have shown the impact of the disease on different domains of the patient's quality of life, insisting on the need of assessing the quality of life as an important outcome associated with the effectiveness of treatment.[21–23] Although 90% of the respondents stated that the possibility of genetic testing was available for PAH patients, it is important to recommend the introduction of recent methods of genetic sequencing in daily practice in view of the growing progress in defining the genetic heterogeneity of the disease[24] and its role in the stratification of risk.[25]

In the section on patient care and available resources, it is worth mentioning the availability of most diagnostic techniques in the center itself. However, in the case of genetic testing, ergospirometry and ventilation/perfusion scintigraphy, the availability was limited, although these procedures could be performed by agreement with other hospitals. European Society of Cardiology clinical practice guidelines (2015) recommend ventilation/perfusion scintigraphy due to its high sensitivity. The low implementation of ventilation/perfusion scintigraphy might be potentially compensated with the use of CT pulmonary angiography which is broadly available in most hospitals, and could be a valid alternative.

This aspect highlights the importance of networking and collaboration among different hospitals and referral centers in order to ensure the access of PAH patients to the resources necessary for proper diagnosis and management of their disease.

Regarding pulmonary vascular reactivity test, epoprostenol was the most frequently used vasodilator. Although adenosine and nitric oxide are approved for this purpose, they were only available in the center itself in 30% and 45% of cases, respectively.

A significant percentage of centers use oral or sublingual sildenafil for acute vasodilator testing in PAH, even though this strategy is not contemplated in GPC guidelines, which recommend inhaled nitric oxide, intravenous epoprostenol, and intravenous adenosine.[26] In 2015, different publications showed a similar vasoreactivity profile of sildenafil when compared to nitric oxide for acute vasodilator testing in PAH.[27] Acute sildenafil administration showed to be safe and simple, with the advantage of no special requirements. Its disadvantage is a slow initial effect (30 minutes) and more prolonged effect (hours) that makes it a less-convenient alternative. It is possible that some centers use sildenafil in special situations for logistical reasons.

According to the results, the pharmacological treatments included in the therapeutic algorithm of ESC/ERS guidelines for pulmonary hypertension were available in the hospitals of the participating specialists. However, there was variability in terms of access to certain pharmacological options among the different centers. It should be noted that 75% of the specialists mentioned that the selective prostaglandin IP receptor agonist selexipag[10] was not available in their hospital. One potential explanation might be that at the time of the survey, the drug had been recently introduced in the Spanish healthcare system.[28] A broader access to other oral drugs, such as ambrisentan, bosentan, and sildenafil was reported. Taking into account the sustainability of the National Healthcare System, the existence of restrictive therapeutic protocols in the hospital was noted, possibly due to budget constraints

and promote the introduction of generic drugs with indication for PAH. Patients could be referred to reference hospitals in order to receive pharmacological treatments and mitigate any access problem. Despite the results, in general terms, patients have access to pharmacological treatments. Also, the access situation could be less restrictive than other European countries.

According to the European Union and Ministry of Health guidelines and recommendations in Spain, lung transplantation, pulmonary angioplasty, septostomy, *etc.* could be performed mainly in specialized HP units. For that reason, the availability in the respondent's centers of surgical options such as atrial septostomy or lung-heart transplantation was limited. As improvement areas, the creation of networks between HP units of different experience and capacity should be promoted in order to share knowledge and practices.

Although there have been important advances in the PAH therapeutic armamentarium, at the time of the survey not all patients respond or maintain a good response to pharmacological treatment. A recent analysis of 1391 patients included in the REHAP registry showed the underuse of lung transplantation for PAH patients.[29] The authors pointed out that, as observed in other respiratory diseases, the use of lung or heart-lung transplantation as a treatment for PAH is restricted to highly selected cases, so that half of the patients potentially eligible for transplant do not have access to it. These outcomes could be improved if the referral to hospitals with lung transplantation program was facilitated for patients in the early stages of the disease.[29]

Access to technical and human resources and to continuing education, the removal of administrative access barriers for drug prescription and the creation of networks between HP units with different experience and capacity, were identified as areas for improvement.

Although the vast majority of the surveyed specialists follow the treatment recommendations of the European Guidelines of PAH, some of them considered that treatment options are conditioned by the existence of restrictive therapeutic protocols in their own hospital.

Limitations

The present results should be interpreted taking into account some limitations of the study, especially quantitative data analysis (*e.g.* NYHA class at diagnosis, numbers and types of patients seen), which are driven by opinion rather than verifiable data. However, the study offers a wide perspective of the current management of adult patients with PAH in our setting.

Conclusions

The analysis of the hospital units dedicated to clinical management of patients with PAH participating in this study, indicates that the majority (90%) are currently implementing ESC/ERS guidelines recommendations for the diagnosis and treatment of pulmonary hypertension. However, more than 60% of respondents mentioned access to technical and human resources, continuing education, and administrative barriers for drug prescription, as areas for improvement.

What is known about the subject?

- PAH management in Spain is mainly undertaken by PH hospital units, where healthcare is provided in accordance with the current standards.
- It is estimated that there are 30–35 active PAH units in Spain (data from the REHAP registry)
- The knowledge of the characteristics and resources available in the units involved in the healthcare of PAH patients is important as a starting point to design improvement strategies.

Does it contribute anything new?

- This is the first analysis in Spain, based on the opinion of healthcare professionals, of human and material resources dedicated to the clinical management of patients with PAH as well as the needs and areas of improvement in the care of these patients.

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Conflicts of interest

J. Segovia-Cubero and J. de Miguel-Díez received consulting fees from GlaxoSmithKline, S.A. during their participation in the study. M. Cevey and L. Gómez are employees of GlaxoSmithKline, S.A. and have stock options in the company.

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REFERENCES

1. Galiè N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. *Rev Esp Cardiol.* 2005;58:523–566.
2. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2004;43(12 suppl S):5S–12S.
3. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and

treatment of pulmonary hypertension of the ESC and the ERS: endorsed by: AEPC, ISHLT. *Eur Heart J*. 2016;37:67–119.
4. McGoon MD, Benza RL, Escribano-Subias P, et al. Pulmonary arterial hypertension: epidemiology and registries. *Am J Coll Cardiol*. 2013;62(25 suppl):D51–D59.
5. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med*. 2006;173:1023–1030.
6. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369:809–818.
7. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest*. 2014;146:449–475.
8. Galie Nea. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373:834–844.
9. Sandoval J, Gomez-Arroyo J, Gaspar J, Pulido-Zamudio T. Interventional and surgical therapeutic strategies for pulmonary arterial hypertension: beyond palliative treatments. *J Cardiol*. 2015;66:304–314.
10. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373:2522–2533.
11. Maron BA, Choudhary G, Khan UA, et al. Clinical profile and underdiagnosis of pulmonary hypertension in US veteran patients. *Circ Heart Fail*. 2013;6:906–912.
12. Deaño RC, Glassner-Kolmin 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;173:887–893.
13. Ryan JJ, Butrous G, Maron BA. The heterogeneity of clinical practice patterns among an international cohort of pulmonary arterial hypertension experts. *Pulm Circ*. 2014;4:441–451.
14. Barberà JA, Escribano P, Morales P, et al. Standards of care in pulmonary hypertension. Consensus statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Cardiology (SEC). *Rev Esp Cardiol*. 2008;61:170–184.
15. Montani D, O'Callaghan DS, Jaïs X, et al. Implementing the ESC/ERS pulmonary hypertension guidelines: real-life cases from a national referral centre. *Eur Respir Rev*. 2009;18:272–290.
16. Taichman DB, McGoon MD, Harhay MO, et al. Wide variation in clinicians' assessment of New York Heart Association/World Health Organization functional class in patients with pulmonary arterial hypertension. *Mayo Clin Proc*. 2009;84:586–592.
17. Pugh ME, Hemnes AR, Trammell A, Newman JH, Robbins IM. Variability in hemodynamic evaluation of pulmonary hypertension at large referral centers. *Pulm Circ*. 2014;4:679–684.
18. Registro Español de Hipertensión Arterial Pulmonar [Internet]. Available at: https://www.rehap.org/ [consulted 29 Apr 2018].
19. Casali L, Carratù P, Sofia M. Clinical variability of respiratory pulmonary hypertension: implications for diagnosis and management. *Multidiscip Respir Med*. 2013;8:72.
20. Escribano Subias P, Barberà Mir JA, Suberviola V. Evaluación diagnóstica y pronóstica actual de la hipertensión pulmonar. *Rev Esp Cardiol*. 2010;65:583–596.
21. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. *Eur Respir Rev*. 2015;24:621–629.
22. Zlupko M, Harhay MO, Gallop R, et al. Evaluation of disease-specific health-related quality of life in patients with pulmonary arterial hypertension. *Respir Med*. 2008;102:1431–1438.
23. Flattery MP, Pinson JM, Savage L, Salyer J. Living with pulmonary artery hypertension: patients' experiences. *Heart Lung*. 2005;34:1431–1438.
24. Austin ED, Loyd JE. The genetics of pulmonary arterial hypertension. *Circ Res*. 2014;115:189–202.
25. Ma L, Chung WK. The genetic basis of pulmonary arterial hypertension. *Hum Genet*. 2014;133:471–479.
26. Preston IR, Klinger JR, Houtches J, Nelson D, Farber HW, Hill NS. Acute and chronic effects of sildenafil in patients with pulmonary arterial hypertension. *Respir Med*. 2005;99:1501–1510.
27. Milger K, Felix JF, Voswinckel R, et al. Sildenafil versus nitric oxide for acute vasodilator testing in pulmonary arterial hypertension. *Pulm Circ*. 2015;5:305–312.
28. Bot Plus [Internet]. Available at: https://botplusweb.portalfarma.com/ [consulted 2017-2018].
29. López-Meseguer M, Quezada C, Ramon M, Lázaro M, Dos L, Lara Aea. Lung and heart-lung transplantation in pulmonary arterial hypertension. *PLoS One*. 2018;13, e0187811.