Comments on the 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension

Introducción

Desde 2011, la Sociedad Española de Cardiología ha tenido una política de apoyo a todas las guías de práctica clínica publicadas por la Sociedad Europea de Cardiología (ESC). Para aumentar la difusión y aplicación de las guías, se han traducido al español y publicado en Revista Española de Cardiología. En colaboración con el Grupo de Trabajo SEC para el manejo de la hipertensión pulmonar, las guías de 2004 y 2009 y el Grupo de Trabajo de la SEC para la elaboración de la guía 2015.

El presente artículo contiene los comentarios sobre las nuevas guías SEC para la diagüstación y tratamiento de la hipertensión pulmonar. Las nuevas guías se producen en coordinación con la Sociedad Europea de Respiración y se han endosadas por otras sociedades europeas. Se siguen y reemplazan las guías de 2004 y 2009. El Grupo de Trabajo SEC formó un grupo de trabajo compuesto por miembros de la Sociedad Española de Cardiología para desarrollar los comentarios en estas guías.

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Las new guidelines on PH establish a new common classification for adults and children, modify the hemodynamic definition of postcapillary PH, and review the new pathophysiological concepts of the condition. They also contain new diagnostic and treatment algorithms, which indicate the need to refer these patients to expert centers for diagnosis and treatment. There are also changes in the assessment of severity of the condition; treatment goals are established, and new drugs are presented, as well as strategies for combination therapy.

Table 1 shows the most important and novel aspects of the guidelines, and Table 2 contains the debatable and undetermined aspects.
Debatable and Undetermined Aspects

Table 2
Debatable and Undetermined Aspects

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<th>Definition and diagnosis</th>
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BNP, brain natriuretic peptide; CTEPH, chronic thrombo-embolic pulmonary hypertension; FC, functional class; PH, pulmonary hypertension; PAH, pulmonary artery hypertension.

is recognized as an excellent tool for early diagnosis and prognostic evaluation.1

Implications for Clinical Practice

In clinical practice, because of the increase in risk factors for PH, clinicians should maintain a high index of clinical suspicion for this entity and monitor a new group of patients more closely. Definite, likely, and possible risk factors have been detailed and updated. Registers have become excellent tools for monitoring the association between new drugs/toxins and PH.

DIAGNOSIS

Important and Novel Aspects

The concept of the “multidisciplinary team” is presented as the basic tool for the correct diagnosis and etiological classification of patients with PH. These teams should include at least 1 cardiologist, 1 pulmonologist, and 1 radiologist with expertise in pulmonary imaging.
In respiratory function testing, the guidelines highlight the role of testing diffusion capacity for carbon monoxide (DLCO). If DLCO is < 45%, thorough investigation must be conducted to identify associated respiratory diseases and to rule out PVOD. A low DLCO is a marker of poor prognosis.

In echocardiography, noninvasive estimation of PAP has been abandoned as a diagnostic criterion. Based on echocardiographic findings, 3 levels are identified for the probability of having PH (low, medium, high). These imply, respectively, no further investigation, a repeat test after a determined period, or further investigation. These levels are divided according to the maximum velocity of tricuspid regurgitation (Table 8a of the guidelines) and the presence of “echocardiographic signs suggesting PH” (Table 8b of the guidelines). Finally, Table 9 contains a suggested overall interpretation of echocardiographic findings in the context of patients at risk of PH and the indications for continuing with the diagnostic algorithm of PH, including right heart catheterization (RHC).

Diagnostic RHC is the definitive test for the diagnosis of PAH and the recommended test to assess therapeutic response. Vasoreactivity testing is indicated for patients with IPAH, HPAH, and DPAH. It should be performed in an expert center, with nitric oxide as the first choice vasodilator.

For the first time, there are highly precise instructions for the correct performance of diagnostic RHC with a meticulous description of how to obtain measurements and ensure maximum precision, indicating which parameters are essential and how they should be measured.

Due to the high prevalence of group 2 PH, the differential diagnosis has been detailed according to a) clinical/echocardiographic classification, and b) recommendations for performing left heart catheterization with determination of LV end-diastolic pressure and coronary angiography. Table 30 of the guidelines summarizes the clinical, echocardiographic, electrocardiographic, and radiological findings that point to left heart disease as the cause of PH.

For the first time, genetic testing has been included in the diagnostic assessment, and the guidelines establish that it should be offered to patients with familial, idiopathic, or drug-related PAH (BMPR2 mutations) and to patients with sporadic or familial PVOD (EIF2AK4 mutations). The guidelines emphasize the importance of prior genetic counselling carried out by a specialized multidisciplinary team in line with the particular laws of each country.

Debatable and Undetermined Aspects

The differential diagnosis between PAH and PH associated with heart failure with a preserved ejection fraction remains a critical point and a difficult decision in everyday clinical practice. The guidelines reflect the usefulness of catheterization with a fluid challenge for patients with a clinical profile that points to group 2 PH and a pulmonary wedge pressure (PWP) of ≤ 15 mmHg. However, it is recognized that the test lacks standardization and that little information is available on its reliability for establishing clear cutoff points. Similarly, exercise catheterization might be a useful tool, but there is no protocol for its use, and the complexity of the procedure means that it is rarely applicable in practice.

Implications for Clinical Practice

Following a stepwise diagnostic approach (groups 2–4), and independently of the suspected etiology, if the probability of PAH is intermediate-high and there are signs of severe PH or right ventricular dysfunction, the patient should be referred to a PH expert center. Likewise, complex techniques requiring a great deal of experience, such as RHC, acute vasoreactivity test, and pulmonary angiography, should be performed in a PH expert referral center.

The concept of “out of proportion” has been abandoned as a key point for referral of patients with a suspected diagnosis from group 2 or 3 to an expert referral center; it is established that patients with severe PH or right ventricular dysfunction should be referred.

In Spain, a founder mutation of the EIF2AK4 gene has been described in association with PVOD in patients of gypsy ethnicity, with several members of each family being affected. This disease has autosomal recessive inheritance. In these patients, disease onset is before 40 years old, usually with a fatal outcome within 2 years after diagnosis. Therefore, in Spain, in patients of gypsy ethnicity being investigated for dyspnea with a family history of PAH and very low DLCO, there should be a high degree of suspicion for this mutation. A genetic study of EIF2AK4 is recommended at the initial assessment, along with adequate genetic counselling and screening of relatives of patients carrying the mutation.

SEVERITY EVALUATION AND PROGNOSIS

Important and Novel Aspects

Patients are classified according to risk into 3 groups, each of which is assigned an estimated 1-year mortality: low-risk (< 5%), intermediate-risk (5%-10%), and high-risk (> 10%). The primary aim is to ensure patients remain in the low-risk group; in fact, the intermediate-risk group is considered suboptimal.

In imaging techniques, particular emphasis is placed on the need for an overall assessment that includes RV systolic function, indirect signs of increased right preload, and parameters of ventricular interdependence. There is emphasis on the importance of an expert echocardiographer performing the general assessment, even more so than specific numerical values. For the first time, cardiac magnetic resonance appears as a potential technique for prognostic assessment.

Debatable and Undetermined Aspects

The arbitrary division into 3 risk groups is a necessary step forward to better determine the minimum thresholds that should be aimed for to change the course of the disease in patients with PAH. However, there is insufficient scientific evidence to support the mortality associated with each risk group or to establish the optimal target values of the different parameters or the relative importance of each of these parameters.

The established cutoff points for prognostic stratification are based on expert opinion and information derived from single-center studies with a small number of patients at the time of diagnosis. The applicability of these cutoff points is unknown when dealing with patients under follow-up and on PH-specific treatment, who are reassessed every 3 to 6 months.

Implications for Clinical Practice

The guidelines expressly open the possibility of not conducting invasive monitoring with routine cardiac catheterization if all other parameters are at low to intermediate risk levels, making it clear that there is no demonstrated increase in survival with regular monitoring with RHC.

TREATMENT

Important and Novel Aspects

Long-term anticoagulation is still recommended for patients with idiopathic, heritable, and anorexigen-associated PAH. Anticoagulation is strongly indicated for patients with indwelling central venous catheters. The potential benefit in combined forms of PAH is unclear and this recommendation has been withdrawn.
Iron deficiency, which is very common in patients with PAH, is associated with reduced exercise capacity and increased mortality, independently of whether or not anemia is present. Intravenous (iv) iron is recommended in patients with severe iron deficiency or those who do not respond to oral therapy.

There are important developments in PAH-specific treatment in these guidelines, with the emergence of new drugs. In particular, a hierarchy has been incorporated, based on the primary endpoints of the clinical trials conducted, with the aim of combining level of evidence and clinical efficacy. Therefore, the treatment algorithm highlights monotherapy or combination drugs with clinical trials in which the primary endpoint was time until deterioration, clinical event, or all-cause mortality.

### Endothelin Receptor Antagonists

The most notable inclusion to the therapeutic arsenal is that of macitentan (a nonselective endothelin antagonist), based on a new trial, with 742 patients and a mean duration of 100 weeks, in which reduction of morbidity and mortality was the primary outcome. Macitentan has lower hepatotoxicity and fewer potential significant drug interactions than other available endothelin receptor antagonists. However, it requires monitoring of hemoglobin concentration, as a reduction to ≤ 8 g/dL was observed in 4.3% of patients receiving 10 mg macitentan.

### Phosphodiesterase Type 5 Inhibitors and Guanylate Cyclase Stimulators

The addition of the intravenous formulation of sildenafil is of particular interest for the critically ill patient or patients who are temporarily unable to tolerate the oral route.

Another drug added to this metabolic pathway is riociguat. Riociguat has a distinct mechanism of action based on stimulation of guanylate cyclase and, therefore, increased production of cyclic guanosine monophosphate (cGMP). The efficacy of riociguat was demonstrated in a clinical trial of classic design in patients with PAH and patients with chronic thrombo-embolic PH (CTEPH).

### Prostacyclin Analogues and Prostacyclin Receptor Agonists

The thermo-stable formulation of iv epoprostenol is a particularly interesting development, as it allows the medication to be changed every 24 to 48 hours.

Treprostinil is available in oral, inhaled, and intravenous formulations, which broadens the therapeutic range of prostanooids. It should be noted that, because the clinical trial with oral treprostinil did not meet the primary endpoint, the recommendation level for this formulation is Iib. Epoprostenol and treprostinil are not dose-equivalent. It is recommended to double or triple the dose when switching from iv epoprostenol to iv treprostinil.

Selexipag (an oral selective prostacyclin receptor agonist) is expected to be added to the therapeutic arsenal, but it has not yet been approved by the European Medicines Agency.

### Combination Therapy

Since the last guidelines in 2009, evidence has increased in favor of combination therapy. In clinical practice, the most common approach is sequential combination therapy, based on previously established treatment goals to achieve higher treatment efficacy and optimize outcomes. The main disease parameters that determine prognosis (Table 13) are considered simultaneously, and treatment is intensified by adding drugs progressively until reaching values that are considered safe (low risk). Currently, intermediate risk is considered an insufficient response and requires an increase in treatment. The sequential combinations that have been demonstrated to reduce morbidity and mortality are macitentan with sildenafil, and selexipag with sildenafil or bosentan. These recommendations are class I in functional class (FC) II-III and class IIa in FC IV. If treatment goals are not met with dual therapy, triple therapy is recommended.

Initial (or upfront) combination therapy is based on the use of 2 drugs from the time of diagnosis. It has recently been demonstrated that the combination of tadalafil and ambrisentan reduces adverse clinical events by 50%; clearly superior than the effect achieved with any monotherapy drug. Therefore, the current recommendation for initial combination therapy with tadalafil plus ambrisentan is class I in FC II-III and IIb in FC IV.

For high-risk patients, initial combination therapy should be considered from the time of diagnosis. In this situation, epoprostenol is an essential component, as it has been demonstrated to reduce mortality in patients in FC IV.

For the first time, there is a separate section specifically for the treatment of the critically ill patient with PAH in the intensive care unit. This includes a description of the recommended monitoring, the drugs of choice, and the recommendation to avoid intubation, because it can trigger irreversible hemodynamic collapse in such patients. In addition, the use of arteriovenous extracorporeal membrane oxygenator (ECMO) and atrial septostomy should be considered as a bridge to transplant or recovery.

Transplant remains a therapeutic option for patients with PAH, and the guidelines highlight the need to refer patients to transplant centers soon after failure of combination therapy and before exhausting the treatment options (triple therapy).

### Debatable and Undetermined Aspects

There is new evidence on supervised exercise training in patients with PAH. However, the best training method and real impact on long-term prognosis are still unknown.

Contraception is essential; however, there is no agreement on the best method. The recommendation is a combination of a barrier method plus an oral contraceptive (progesterone-only preparations) or a levonorgestrel-releasing intrauterine device. In the case of an intrauterine device, there must be an available anesthetic team trained to manage a potential vasovagal reaction in the patient with PAH, induced by manipulation of the uterine cervix.

Most transplants are bilateral lung transplants, and combined heart and lung transplant is indicated only for patients with irreversible RV or left ventricular dysfunction, or for patients with complex congenital heart diseases. However, clear limits are yet to be established indicating when ventricular dysfunction is irreversible and a heart and lung transplant is indicated.

### Implications for Clinical Practice

In the absence of direct comparisons between different drugs, none can be claimed to be superior. Therefore, an individualized drug choice is advised, taking into account adverse effects and drug interactions.

Specifications have been included on the management of the most common complications in patients with PAH: a) atrial arrhythmia, a marker of poor prognosis that requires early treatment to recover and maintain sinus rhythm (electrical cardioversion or ablation in flutter); b) pulmonary artery aneurisms, whose symptoms depend on the structure they compress and which have an implicit risk of rupture or dissection; and c) hemoptysis, with a prevalence of 1% to 6%.

Given the complexity of the treatment algorithm and the specialization of the treatments, patients with PAH should be managed in an expert referral center that can provide them with all treatment options in a timely manner.
The treatment algorithm is designed only for patients with PAH and, in particular, those with HPAH, IPAH, DPAH, congenital heart disease, and connective tissue disease.

**Experimental Areas of Treatment for Pulmonary Hypertension Not Included in the Routine Recommendations.**

The use of catheter-based renal denervation as a treatment for PAH is a new line of treatment that is taking its first steps with studies in animal models. It has been determined that the biological plausibility of catheter-based renal denervation is not entirely evident; the main pathophysiological mechanism involved in PAH is not vasoconstriction, but vascular remodeling due to fixed obstructive lesions with proliferation of endothelial and smooth muscle cells. It is unlikely that catheter-based renal denervation could induce reverse remodeling of severe obstructive lesions in the distal pulmonary arteries. Attention must be paid to progress in this area of sympathetic nervous system modification in pulmonary hypertension, which at present is a working hypothesis.

**SPECIFIC SUBGROUPS OF PULMONARY ARTERIAL HYPERTENSION**

**Important and Novel Aspects**

Pediatric PH has been incorporated in the classification of PH, with modifications to each group to reflect the uniqueness of PH in this age group. Prognostic stratification is complicated, and there is little information available; factors associated with increased mortality risk include FC III/IV, high concentrations of brain natriuretic peptide (BNP), delayed growth, mPAP/systemic arterial pressure ratio > 0.75, right atrial pressure > 10 mmHg, and a pulmonary vascular resistance index > 20 WU/m². The 6-minute walking test has no prognostic value in children.

Bosentan is available as a pediatric formulation. Sildenafil has been approved in Europe for children aged 1 to 17 years, but attention is drawn to the increased mortality observed with its use at high doses; maximum doses, which must not be exceeded, are indicated according to the child’s weight. Children have also been treated with intravenous epoprostenol and subcutaneous treprostinil, with favorable outcomes. As is the case in adults, combination therapy and management of such patients in an expert referral center are recommended. Bilateral lung transplant is the last treatment option.

In PH associated with adult congenital heart disease, a change has been made to the classification, and congenital heart disease is included in groups 1, 2, and 5. Among the therapeutic considerations, the indications for anticoagulation are highlighted: it is restricted to patients with atrial arrhythmias or pulmonary artery thrombosis in the absence of severe hemoptysis. Supplementary oxygen is indicated if it leads to a clinical improvement and improved peripheral saturation. Iron supplementation should be considered in the presence of iron deficiency, and finally, combination therapy is indicated in these patients.

In the case of PH associated with connective tissue disease, the most novel aspect is PAH screening in scleroderma, with recommended annual echocardiogram, biomarkers, and DLCO as part of the follow-up for asymptomatic patients. Tables 9 and 10 of the web addenda give more details of the proposed screening. Lung transplant is possible in patients with scleroderma, but they must be referred early, as they require a specific workup for gastrointestinal, renal, and cutaneous complications.

In portopulmonary PH, screening with echocardiography is still recommended for all patients who are candidates for liver transplant. Likewise, liver transplant is still contraindicated in the presence of severe PH. There have been reports of experience with all PH drugs, and the aim is to reduce mPAP to < 35 mmHg and PVR to < 3 WU before transplant. This should be managed in a center with expertise in liver transplantation and PH.

In PVOD, the main development is the discovery of bi-allelic EIF2AK4 mutations in the familial forms of the disease. This diagnosis remains highly complicated. The key findings are marked hypoxemia with low DLCO, occasionally clubbing, and typical findings on computed tomography and in bronchoalveolar lavage. Patients must be referred for transplant at the time of diagnosis, as the prognosis is unfavorable and there is no specific treatment.

**Debatable and Undetermined Aspects**

Systemic-to-pulmonary shunt closure in the presence of PH remains controversial. Table 24 of the guidelines contains recommended limits based on PVR. The text makes reference to existing gaps regarding the indications for correction of the anomaly being based on the response to vasoreactivity testing, the closure test, or a pulmonary biopsy result. It is stressed that the treat-to-close strategy (administering treatment to obtain PH figures that permit closure of the defect) is not supported by current data. Lung transplant with defect closure is indicated in simple congenital heart disease; combined heart and lung transplant is indicated in complex congenital heart disease. It is extremely difficult to ascertain the ideal time for transplant.

**Implications for Clinical Treatment**

Care must be taken in excluding congenital heart disease. The difficulties in detecting patent ductus arteriosus, venous sinus interatrial communication, and partial anomalous pulmonary venous drainage can lead to the incorrect diagnosis of IPAH.

Pulmonary hypertension in scleroderma must always be investigated to avoid incorrect diagnosis, as it can fit into group 1, 2, or 3. PVOD has also been described in patients with scleroderma.

**PULMONARY HYPERTENSION IN GROUPS 2 AND 3**

Group 2 PH is most common, followed by group 3. The presence of PH in heart disease or lung disease implies a poor prognosis, and the main treatment indication is to optimize treatment of the underlying condition.

In group 2 or 3, in cases of severe PH unexplained by the severity of the underlying disease, other factors that could increase pulmonary pressure must be ruled out. There are frequently multifactorial associations such as heart failure with preserved ejection fraction, sleep apnea, obesity hypoventilation syndrome, COPD, and pulmonary embolism.

**Important and Novel Aspects**

A new hemodynamic classification is proposed for PH associated with heart disease (Table 3). The terms “isolated post-capillary PH” and “combined precapillary and postcapillary PH” are presented. The guidelines introduce the use of DPG (the difference between diastolic pulmonary artery pressure and mean pulmonary wedge pressure) above or below 7 mmHg, and PVR above or below 3 WU as a method to characterize the 2 subgroups. Patients with group 2 severe precapillary PH require referral to an expert center for individualized assessment.

In group 3 PH, the main development is the hemodynamic classification of PH severity and the indications for referral to an expert center in the presence of severe PH and right ventricular dysfunction.
Debatable and Undetermined Aspects

Diastolic pressure gradient is less dependent than transpulmonary gradient on changes in cardiac output and wedge pressure. The results of different publications are contradictory on the prognostic value of DPG in patients with PH and left heart disease. Furthermore, when the subgroup of patients who are candidates for heart transplant are analyzed, DPG lacks prognostic value. Therefore, the use of DPG and the withdrawal of the transpulmonary gradient in diagnostic algorithms may have been premature and require revalidation.

The use of pulmonary vasodilators specifically approved in PAH is categorically discouraged. However, the usefulness of these drugs in reducing pulmonary resistance and allowing heart transplant in candidates with significant PH should be noted.12

Implications for Clinical Practice

It is notable that no drug has been demonstrated to be effective in the treatment of group 2 and 3 PH. Studying pulmonary vasoreactivity and temporarily modifying it has prognostic implications only for patients who are candidates for transplant of ventricular assistance.

GROUP 4 PULMONARY HYPERTENSION

Important and Novel Aspects

There are no reliable epidemiological data: in the United Kingdom, incidence is estimated at 5 cases/million/y; in Spain, the incidence in 2013 was 1.29 cases/million/y, showing a problem of underdiagnosis in Spain.

Diagnostic evaluation should be carried out after a period of 3 months of effective anticoagulation. The diagnosis is based on the finding of perfusion defects on V/Q scan in the presence of precapillary pulmonary hypertension.

The treatment of choice is surgical pulmonary endarterectomy (PEA). Surgical assessment should be carried out in an expert referral center by a multidisciplinary team; the involvement of a specialized surgeon is essential. Given the low mortality in recent series, the indications for surgery have been extended to include patients in FC II. After PEA, patients must be followed-up at an expert CTEPH center, and at least 1 hemodynamic assessment should be considered at 6 to 12 months postsurgery. Pulmonary angioplasty is presented as an adjuvant treatment for patients who are not candidates for surgery. This interventional procedure should only be performed in centers with ample experience in the management of CTEPH.

For patients with persistent PH after PEA or who are not candidates for PEA, medical treatment with riociguat is the first choice (IB recommendation).

Debatable and Undetermined Aspects

Systematic screening of CTEPH in all patients after a pulmonary embolism is discouraged; it should be performed in those with persistent exertional dyspnea (recommendation Ila). Indications are lacking for a follow-up structure for patients with pulmonary embolism, to avoid underdiagnosis of CTEPH.

Implications for Clinical Practice

All patients with CTEPH should be referred to an expert center for surgical feasibility evaluation. Since September 2015, 2 national referral centers in Spain have been authorized for evaluation of such patients (Hospital 12 de Octubre in Madrid and Hospital Clinic in Barcelona). In Spain, the mortality from PEA between 2006 and 2013 was 3.3%, and survival is higher in patients undergoing surgery than in those receiving medical treatment.13

In Spain, pulmonary angioplasty has started to develop, with results comparable to those described in the literature.14

PULMONARY HYPERTENSION REFERRAL CENTRE

Throughout the guidelines, there are constant references to the need to assess patients in expert referral centers. This section describes the characteristics required for a referral center: a) a minimum volume of patients, b) available staff and technology, c) a working method, d) a communication network with other hospitals, and e) research and teaching.

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CONFLICTS OF INTEREST

None declared.

REFERENCES


