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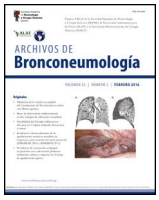

Special article

Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Summary of Recommendations☆

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ABSTRACT

Pulmonary hypertension is a hemodynamic disorder defined by abnormally high pulmonary artery pressure that can occur in numerous diseases and clinical situations. The causes of pulmonary hypertension are classified into 5 major groups: arterial, due to left heart disease, due to lung disease and/or hypoxemia, chronic thromboembolic, with unclear and/or multifactorial mechanisms. This is a brief summary of the Guidelines on the Diagnostic and Treatment of Pulmonary Hypertension of the Spanish Society of Pulmonology and Thoracic Surgery. These guidelines describe the current recommendations for the diagnosis and treatment of the different pulmonary hypertension groups.

Guía de diagnóstico y tratamiento de la hipertensión pulmonar: resumen de recomendaciones

Palabras clave:
Hipertensión pulmonar
Hipertensión arterial pulmonar
Hipertensión pulmonar tromboembólica crónica
Circulación pulmonar
Guía clínica

RESUMEN

La hipertensión pulmonar es un trastorno hemodinámico definido por el aumento anómalo de la presión arterial pulmonar, que puede presentarse en numerosas enfermedades y situaciones clínicas. Las causas de hipertensión pulmonar se clasifican en 5 grandes grupos: arterial, debida a cardiopatía izquierda, debida a enfermedad pulmonar y/o hipoxemia, tromboembólica crónica y de mecanismo no establecido y/o multifactorial. El presente documento expone de forma resumida las recomendaciones de la Guía de Diagnóstico y Tratamiento de la Hipertensión Pulmonar de la Sociedad Española de Neumología y Cirugía Torácica. En dicha guía se presentan las pautas actuales de diagnóstico y tratamiento de los distintos grupos de hipertensión pulmonar.

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Table 1
Levels of Evidence and Class of Recommendation Used in the Guidelines.

Levels of evidence	
A	Data derived from multiple randomized clinical trials or meta-analysis
B	Data derived from a single randomized or large non-randomized studies
C	Consensus of expert opinion, small or retrospective studies, or patient registries
Classes of recommendation	
I	Evidence and/or general agreement that a particular treatment or procedure is beneficial, useful, or effective
II	Conflicting evidence and/or diverging opinions about the usefulness/effectiveness of a given treatment or procedure
IIa	Evidence/opinion tends toward usefulness/effectiveness
IIb	Usefulness/effectiveness is less supported by evidence/opinion
III	Evidence or general agreement that a particular treatment or procedure is not useful/effective and, in some cases, may be harmful

Introduction

This document is a summary of the recommendations of the Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension prepared by the Spanish Society of Pulmonology and Thoracic Surgery,[1] that was drawn from the clinical practice guidelines of the European Society of Cardiology and the European Respiratory Society.[2] For more details, please refer to the original guidelines,[1] (https://issuu.com/separ/docs/normativa_70?e=3049452/44188557). The levels of evidence and class of recommendation used are set out in Table 1.

Definition and Classification

Pulmonary hypertension (PH) is a hemodynamic, pathophysiological disorder defined by elevated mean pulmonary arterial pressure (mPAP) ≥25 mmHg, measured by right heart catheterization (RHC).[2] PH can occur in various clinical processes, that can be classified into 5 groups (Table 2).

Diagnosis of Pulmonary Hypertension

Detection

Transthoracic echocardiography (TTE) is the main tool for the early detection and screening of PH. The probability of PH according to TTE findings is shown in Table 3.

TTE screening for PH is recommended in asymptomatic subjects in the following risk groups:

- Patients with systemic sclerosis [I, B].
- First-degree relatives of patients with a diagnosis of hereditary pulmonary arterial hypertension (PAH) [I, C].
- Patients with portal hypertension who are candidates for liver transplantation [I, B].

In other cases, TTE will be performed on the basis of clinical suspicion.

General Approach to Diagnosis

The diagnostic algorithm of PH is shown in Fig. 1. TTE will be performed if PH is suspected. If the probability of PH is intermediate or high, left heart disease (PH group 2) and chronic respiratory disease (PH group 3) will be ruled out. Patients in these PH groups or those with severe right ventricular dysfunction will be referred to an expert in PH[2] [IIa, C]. When PH has been ruled out in groups 2 and 3, ventilation–perfusion lung scintigraphy will be used to rule out thromboembolic disease. If perfusion defects are observed on the ventilation–perfusion scintigraphy, a study for probable chronic thromboembolic pulmonary hypertension will be performed. Hemodynamic diagnosis with RHC will be carried out in an expert PH unit [I, C]. If PAH is confirmed, the subtype should be identified.

Pulmonary Arterial Hypertension

Evaluation

In patients with idiopathic, hereditary, or drug-related PAH, a vasodilator test with inhaled nitric oxide or iv epoprostenol will be performed during the RHC diagnostic procedure [I, C]. The test is positive if mPAP drops ≥10 mmHg to reach a value ≤40 mmHg, with no reduction in cardiac output [I, C]. The subtype will be identified by contrast echocardiography, autoimmunity testing, hepatotropic virus serology, and HIV serology (Fig. 1). If there is a family history of PH, or if it is suspected, a study to identify BMPR2 gene mutations is advisable.[3–5]

The diagnosis of pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) is based on clinical data, very low carbon dioxide diffusing capacity, severe hypoxemia, and consistent findings on high-resolution computed tomography (HRCT).[6] It can also be diagnosed from the presence of EIF2AK4 gene mutations.[6]

A set of variables associated with survival are used for evaluating prognosis[2] (Table 4). For monitoring, clinical parameters and more easily performed tests (functional class [FC], 6-minute walk test, ECG, clinical laboratory tests) should be evaluated every 3–6 months, while the more complex procedures should be performed every 6–12 months,[7] or in case of clinical deterioration [I, C].

Treatment

General Measures and Support

General therapeutic measures for PAH are listed in Table 5. Diuretics are indicated in patients with right ventricular failure and water retention [I, C]. Loop diuretics or aldosterone antagonists should be used.[2] Anticoagulation with vitamin K antagonists is recommended in idiopathic and hereditary PAH, and PAH caused by anorectics [IIb, C]. Oxygen therapy is recommended if PaO_2 is <60 mmHg [I, C]. It may also be considered as an option for correcting desaturation during exercise.[2] Regular monitoring of iron levels is recommended, and supplements should be administered if necessary.

Specific Treatment

Specific drugs for the treatment of PAH include (Table 6):

- Calcium channel blockers: indicated for use in patients with idiopathic PAH and positive vasodilator test [I, C]. High-dose nifedipine, diltiazem and amlodipine are recommended.[8]
- Endothelin receptor antagonists, including ambrisentan, bosentan, and macitentan. Ambrisentan and bosentan can cause liver toxicity, so monthly monitoring of liver enzymes is required. Macitentan carries a risk of anemia, and regular monitoring of hemoglobin levels is recommended.
- Phosphodiesterase type 5 (PDE5) inhibitors and soluble guanylate cyclase (sGC) stimulators: available PDE5 inhibitors are sildenafil and tadalafil, and the only available sGC stimulator is riociguat. The concomitant administration of PDE5 inhibitors and sGC stimulators is contraindicated.
- Prostacyclin analogs and prostacyclin receptor agonists: available prostacyclin analogs include epoprostenol, administered via

Table 2
Classification of Pulmonary Hypertension (European Society of Cardiology/European Respiratory Society, 2015).

1. Pulmonary arterial hypertension (PAH)
- *1.1. Idiopathic*
- *1.2. Hereditary*
  - 1.2.1. BMPR2 mutation
  - 1.2.2. Other mutations
- *1.3. Induced by drugs and toxins*
- *1.4. Associated with:*
  - 1.4.1. Connective tissue disease
  - 1.4.2. HIV infection
  - 1.4.3. Portal hypertension
  - 1.4.4. Congenital heart disease
  - 1.4.5. Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
- *1′.1. Idiopathic*
- *1′.2. Hereditary*
  - 1′.2.1. EIF2AK4 mutation
  - 1′.2.2. Other mutations
- *1′.3. Induced by drugs, toxins, and radiation*
- *1′.4. Associated with:*
  - 1′.4.1. Connective tissue disease
  - 1′.4.2. HIV infection

1″. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
- *2.1. Left ventricular systolic dysfunction*
- *2.2. Left ventricular diastolic dysfunction*
- *2.3. Valvular disease*
- *2.4. Congenital/acquired obstruction of the left ventricular inflow/outflow tract and congenital cardiomyopathy*
- *2.5. Congenital or acquired pulmonary vein stenosis*

3. Pulmonary hypertension due to respiratory disease and/or hypoxemia
- *3.1. Chronic obstructive pulmonary disease*
- *3.2. Diffuse interstitial lung disease*
- *3.3. Other lung diseases with mixed restrictive and obstructive pattern*
- *3.4. Sleep disordered breathing*
- *3.5. Alveolar hypoventilation*
- *3.6. Chronic exposure to high altitudes*
- *3.7. Lung development disorders*

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
- *4.1. Chronic thromboembolic pulmonary hypertension*
- *4.2. Other pulmonary artery obstructions*
  - 4.2.1. Angiosarcoma
  - 4.2.2. Other intravascular tumors
  - 4.2.3. Arteritis
  - 4.2.4. Congenital pulmonary artery stenosis
  - 4.2.5. Parasitosis (hydatid disease)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- *5.1. Hematologic diseases: hemolytic anemia, myeloproliferative disorders, splenectomy*
- *5.2. Systemic diseases: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis*
- *5.3. Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders*
- *5.4. Other: pulmonary tumor thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension*

Table 3
Probability of Pulmonary Hypertension Based on Transthoracic Echocardiography Results.

Low	TRV ≤2.8 m/s or not measurable
Intermediate	TRV 2.9–3.4 m/s; or VRT ≤2.8 m/s or not measurable, in the presence of other ultrasonographic signs of pulmonary hypertension
High	TRV >3.4 m/s; or TRV 2.9–3.4 m/s, in the presence of other ultrasonographic signs of pulmonary hypertension

*** Other echocardiographic signs that indicate pulmonary hypertension:**
- *Ventricles*
  - Basal RV/LV ratio >1.0
  - Flattening of interventricular septum (LV eccentricity index >1.1 in systole or diastole)
- *Pulmonary artery*
  - Doppler acceleration time of the RV outflow tract <105 ms and/or mesosystolic notch
  - Pulmonary regurgitation velocity in protodiastole >2.2 m/s
  - PA diameter >25 mm
- *Inferior vena cava and right atrium*
  - Inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% in deep inspiration or <20% in normal inspiration)
  - Right atrium area (end systolic) >18 cm^2

PA: pulmonary artery; RV, right ventricle; LV, left ventricle; TRV: tricuspid regurgitation velocity.

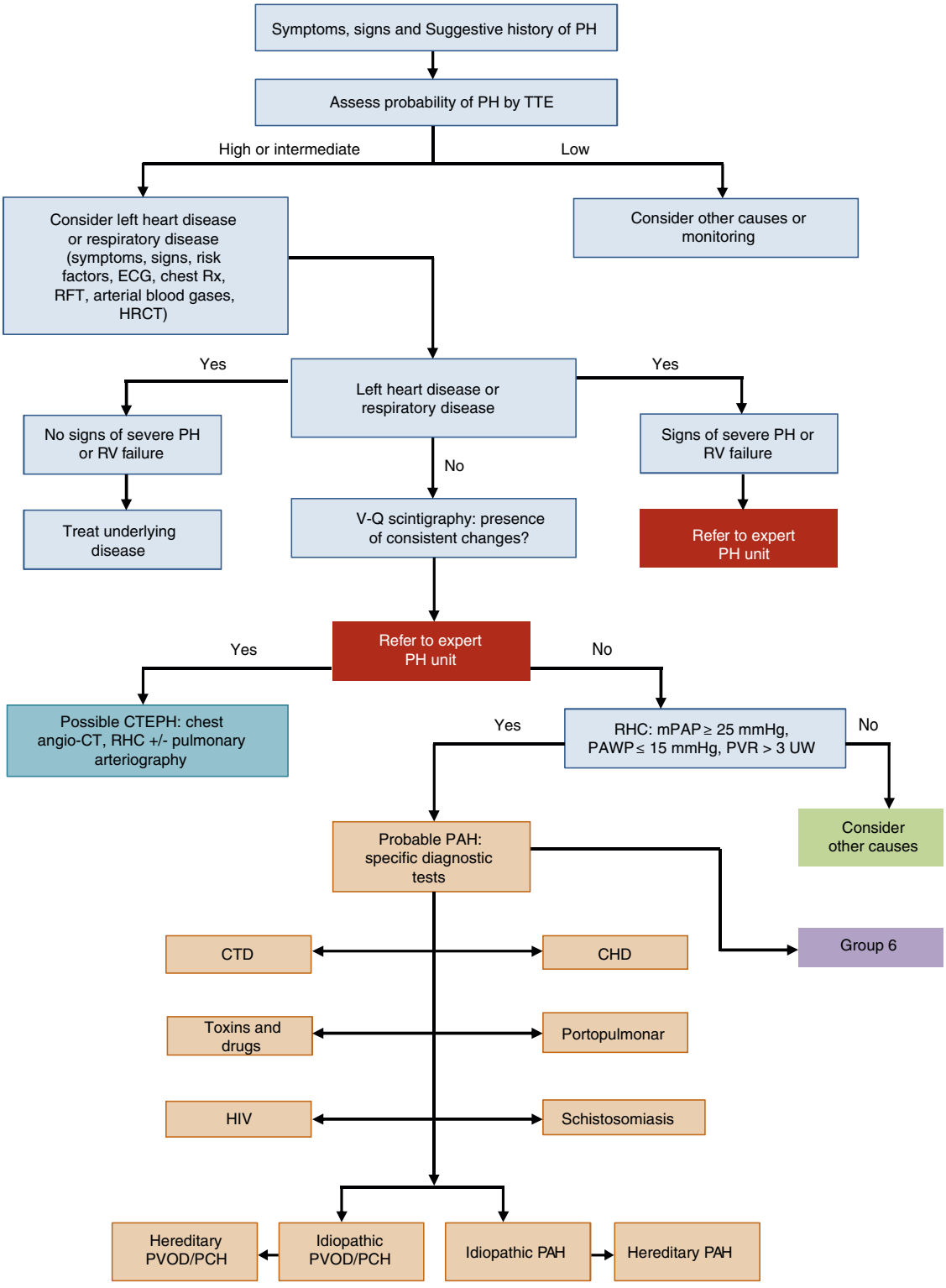

Fig. 1. Diagnostic algorithm for pulmonary hypertension.
CHD: congenital heart disease; CT: computed tomography; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; HIV: human immunodeficiency virus; HRCT: high-resolution computed tomography; mPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary arterial wedge pressure; PCH: pulmonary capillary hemangiomatosis; PH: pulmonary hypertension; PVOD: pulmonary veno-occlusive disease; PVR: pulmonary vascular resistance; RFT: respiratory function tests; RHC: right heart catheterization; RV: right ventricle; Rx: chest X-ray; TTE: transthoracic echocardiography; V-Q: ventilation–perfusion; WU: Wood units.

Table 4
Prognostic Evaluation in Pulmonary Arterial Hypertension.

Prognostic Determinant	Risk		
	Low	Intermediate	High
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
Functional class	I, II	III	IV
Distance walked on 6MWT	>440 m	165–440 m	<165 m
Cardiopulmonary exertion test	VO_2-peak >15 mL/kg/min (>65% ref.) VE/VCO_2 <36	VO_2-peak 11–15 mL/kg/min (35–65% ref.) VE/VCO_2 36–44.9	VO_2-peak <11 mL/kg/min (<35% ref.) VE/VCO_2 ≥45
BNP or NT-proBNP	BNP<50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging techniques (echocardiography, MRI)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 Without or with minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60%

6MWT: 6-minute walk test; BNP: brain natriuretic peptide; CI: cardiac index; MRI: magnetic resonance imaging; NT-proBNP: N-terminal prohormone brain natriuretic peptide; RA: right atrium; RAP: right atrial pressure; SvO_2: oxygen saturation of mixed venous blood; VE/VCO_2: ratio between minute ventilation and CO_2 production; VO_2-peak: peak oxygen uptake.

Table 5
General Therapeutic Measures in Pulmonary Arterial Hypertension.

Recommended measures [I]
- Avoid pregnancy
- Prevention of infections
- Psychosocial support

Measures that should be taken into consideration [class IIa]
- Supervised training [level of evidence B]
- Oxygen therapy during long flights
- Elective surgery should be carried out in centers with experience in pulmonary hypertension

Measures that could be taken into consideration [class IIb]
- Genetic counseling in specialized units of patients or family members with mutations associated with PAH or PVOD
- Avoid drugs that can aggravate PH (nasal decongestants and beta-blockers)
- Diet: advise a daily salt intake of <5 g (equivalent to 2 g sodium), particularly in patients with right heart failure. If RHF is severe or in case of hyponatremia, reduction of water intake to <1.5–2 L/day is also advisable.

Inadvisable activities [III]
- Strenuous physical activity
- Being at altitudes above 1500–2000 m without supplemental oxygen

PVOD: pulmonary veno-occlusive disease; PAH: pulmonary arterial hypertension. All recommendations have a level of evidence C unless otherwise indicated.

continuous iv infusion; iloprost, administered by inhalation; and treprostinil, administered in a continuous subcutaneous microinfusion pump. Inhaled treprostinil has also been shown to be beneficial[9] (Table 4). Selexipag is a prostacyclin receptor agonist that is administered orally.[10]

Invasive Treatments

- Atrial septostomy: indicated in patients with FC IV, with right ventricular failure,[11] or as a bridge treatment in patients waitlisted for transplantation [IIb, C]. This procedure can be performed in hospitals with experience. It should be avoided in patients with right atrial pressure >20 mmHg or SaO_2 <85% breathing room air.
- Lung transplantation: the most common procedure is double lung transplantation. This is indicated in young patients without associated comorbidity who do not respond fully to medical treatment[2] [I, C]. This is the treatment of choice in PVOD and PCH.

Therapeutic Strategy

The therapeutic strategy in PAH is based on 4 components (Fig. 2):

Establish therapeutic objectives: the main aim is to ensure that the patient's risk of death is low (Table 4) [I, C]. Characteristics of a low-risk profile include good tolerance to exertion, quality of life, and right ventricular function. The risk will be defined at the beginning, before starting treatment, and in the periodic monitoring visits [I, C].

Initial approach: this includes general measures (Table 5) and supportive therapy. Hemodynamic diagnosis with vasodilator test should be performed in an expert PH unit [I, B], since the result will help define the risk profile and establish the course of treatment.

Initial treatment: in patients with positive vasodilator response, treatment will begin with high-dose calcium channel blockers. If clinical response at 3 months is inadequate, other specific drugs will be used.

Patients with a low or intermediate risk with a negative vasodilator response will begin treatment with specific drugs in monotherapy or combination (Fig. 2). Endothelin receptor antagonists, PDE5 inhibitors and sGC stimulators in monotherapy have been effective in patients with FC II and III. Prostanoids have been evaluated in patients with FC III. The choice of drug is based on the route of administration, safety profile, possible interactions with other drugs, comorbidities, the amount and quality of the available evidence, patient preferences, experience of the physician, and cost.

If combined treatment is selected from the outset, the only combination that has shown superiority to single-agent therapy is ambrisentan plus tadalafil[12] [I, B].

In patients with a high-risk profile or FC IV, the treatment of choice is intravenous epoprostenol[13] [I, A]. Evidence shows that combined initial treatment with epoprostenol plus 1 or 2 drugs is effective[14] [IIa, C].

Response assessment: response to treatment at 3–4 months will be evaluated [I, C]. If response is unsatisfactory, a second or third drug will be added, and possible referral of the patient for lung transplant evaluation will be considered.[2] All patients should be followed periodically in an expert PH unit. Visit intervals will be established on the basis of disease severity, but should never

Table 6
General Recommendations for Single-agent Treatment of Pulmonary Arterial Hypertension.

		Route of Administration	Dose	Class of Recommendation/Level of Evidence[a]					
				FC II		FC III		FC IV	
Calcium channel blockers (amlodipine, diltiazem, nifedipine)		VO	Nifedipine, 120–240 mg/day Amlodipine, 20 mg/day Diltiazem, 240–720 mg/day	I	C[b]	I	C[b]		
Endothelin receptor antagonists	Ambrisentan	VO	5–10 mg/day	I	A	I	A	IIb	C
	Bosentan	VO	125 mg/12 h	I	A	I	A	IIb	C
	Macitentan[c]	VO	10 mg/day	I	B	I	B	IIb	C
Phosphodiesterase-5 inhibitors	Sildenafil	VO	20 mg/8 h	I	A	I	A	IIb	C
	Tadalafil	VO	40 mg/day	I	B	I	B	IIb	C
Soluble guanylate cyclase stimulators	Riociguat	VO	2.5 mg/8 h	I	B	I	B	IIb	C
Prostacyclin analogs	Epoprostenol[c]	IV	20–40 ng/kg/min			I	A	I	A
	Iloprost	INH	2.5–5 μg/3–4 h			I	B	IIb	C
	Treprostinil	SC	20–80 ng/kg/min			I	B	IIb	C
		INH	54 μg/6 h			I	B	IIb	C
IP prostacyclin receptor agonists	Selexipag[c]	VO	1600 μg/12 h	I	B	I	B		

INH: inhaled; IV: intravenous; SC: subcutaneous; VO: oral.
[a] See Table 1.
[b] Only for those patients with positive vasodilator test.
[c] Drug that has demonstrated delay in time to clinical deterioration as a primary objective in a clinical trial, or the reduction of all-cause death.

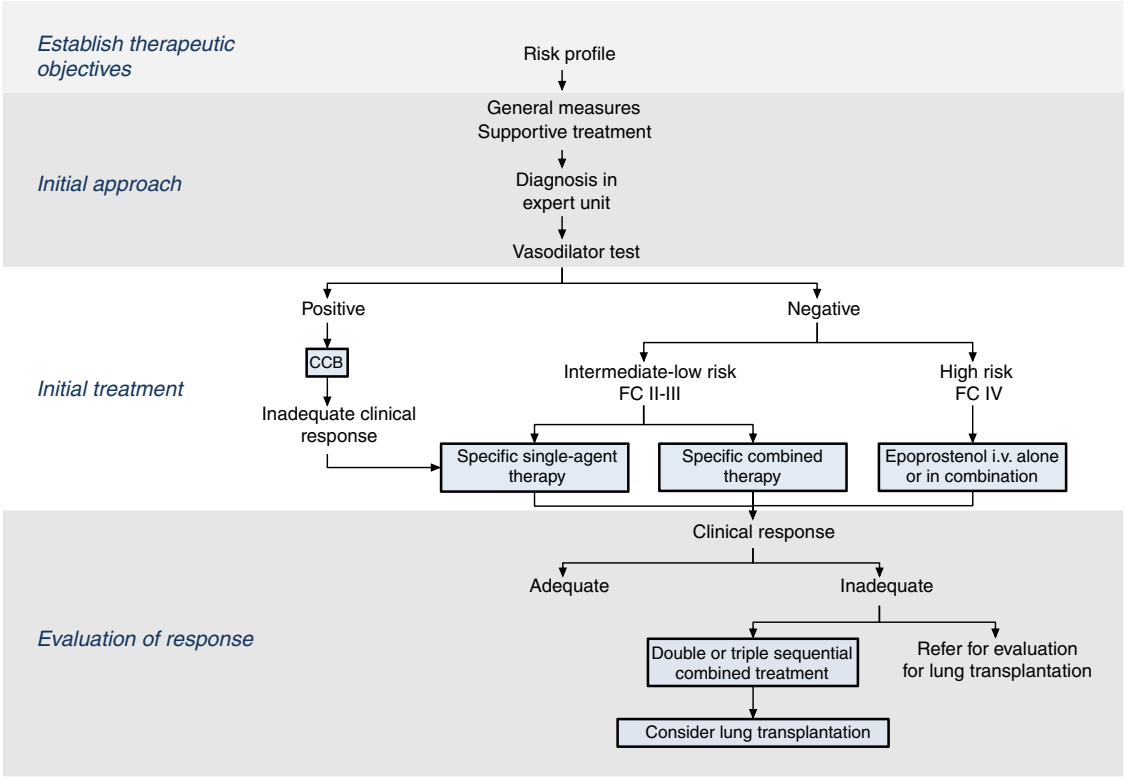

Fig. 2. Therapeutic algorithm for pulmonary arterial hypertension. CCB: calcium channel blockers; FC: functional class.

be longer than 6 months, even in patients with satisfactory clinical response.[2]

Subtype Considerations

Congenital Heart Disease

Congenital heart diseases are included in PH groups 1, 2, 3, and 5, depending on the underlying mechanism. Table 7 lists the PAH classifications associated with congenital heart disease and Table 8 summarizes recommendations for pharmacological treatment. The following limits are proposed for systemic-pulmonary shunt ligation [IIa, C]: it is indicated if pulmonary vascular resistance is <4 Wood units·m^2 and contraindicated for >8 Wood units·m^2. Intermediate situations will be assessed individually.[15]

Connective Tissue Diseases

PAH associated with systemic sclerosis is the most common presentation.[16] Annual screening with TTE and carbon dioxide

Table 7
Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease.

1. Eisenmenger's syndrome	Includes large intra- and extracardiac defects which begin with systemic-to-pulmonary shunt and eventually progress to a severe elevated PVR and systemic-pulmonary shunt ligation or bidirectional shunt. Cyanosis, multiple organ failure and polycythemia tend to occur
2. PAH associated with prevalent systemic-pulmonary shunts	Correctable[a] Not correctable Includes moderate or large defects. PVR is slightly or moderately high and systemic-to-pulmonary shunt prevails. Cyanosis at rest is not characteristic
3. PAH with small defects or chance finding[b]	Marked elevation of PVR in presence of small cardiac defects (usually interventricular septal defects <1 cm or interatrial septal defects <2 cm in diameter, as assessed by echocardiography). The clinical picture is very similar to that of idiopathic PAH. Defect closure is contraindicated.
4. PAH associated with CHD with corrected heart defect	CHD is repaired but PAH persists immediately after correlation or recurs or develops months or years after the procedure.

CHD: congenital heart disease; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance.
[a] With surgery or percutaneously.
[b] Size refers to adult patients. However, even in adults the diameter may be insufficient to define the hemodynamic significance of the defect or the pressure gradient, the directionality or size of the shunt, so pulmonary and systemic flow ratio must be taken into account.

Table 8
Pharmacological Treatment of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease.

1. Anticoagulation is restricted to patients with atrial arrhythmias and/or thrombosis of the pulmonary arteries [IIb, C]
2. Supplemental oxygen is indicated if it improves clinical status and SaO_2 [IIa, C]
3. Iron supplementation should be considered in the presence of iron deficiency [IIb, C]
4. Bosentan is the treatment of choice in patients with Eisenmenger's syndrome [I, B]
5. Combined treatment with ERA, PDE5 inhibitors, and/or prostanoids is indicated [IIa, C]
6. Lung transplantation with the closure of the defect is indicated in congenital heart disease, with heart-lung transplantation in complex cases.

ERA: endothelin receptor antagonists; PDE5 inhibitors: phosphodiesterase type 5 inhibitors; SaO_2: oxygen saturation in arterial blood.
[Class of recommendation, level of evidence].

diffusing capacity is recommended in patients with systemic sclerosis[17] [I, C]. In other connective tissue diseases, TTE is recommended in symptomatic individuals. Chest HRCT is useful for evaluating the presence of interstitial lung disease and PVOD.[18] RHC is recommended whenever PAH is suspected [I, C]. Patients with scleroderma and mPAP 21–24 mmHg should be monitored due to their high risk of developing PAH.[19]

Patients with connective tissue diseases and PAH should be treated according to the general PAH algorithm [I, C]. Oral anticoagulation is associated with a worse prognosis,[20] so it should only be used in patients prone to thrombophilia (antiphospholipid antibodies)[21] [IIb, C]. Immunosuppressive therapy may benefit patients with PAH associated with systemic lupus erythematosus or mixed connective tissue disease.[22]

Portopulmonary Hypertension

Portopulmonary hypertension is defined as combined portal and pulmonary hypertension. Patients with portopulmonary hypertension have higher mortality than patients with idiopathic PAH,[23,24] so referral to expert centers is recommended [I, C]. The use of anticoagulants [III, C] and beta-blockers is not recommended.[25] Portopulmonary hypertension is a major risk factor in liver transplantation,[26] so it must be ruled out by TTE in all transplant candidates [I, B] and these results must be confirmed with a hemodynamic study. If mPAP is <35 mmHg, transplantation can be considered[26] [IIb, C]. If mPAP is ≥35 mmHg, specific therapy with reevaluation at 3 months is recommended. If PAP remains high despite treatment, liver transplantation is contraindicated [III, C].

HIV Infection

TTE to detect PAH should be performed in cases of unexplained dyspnea [III, C]. Anticoagulation is not recommended because of the risk of bleeding and possible drug interactions [III, C]. Account should be taken of interactions between PDE5 inhibitors and some antiretroviral drugs.

Pulmonary Veno-occlusive Disease and Pulmonary Capillary Hemangiomatosis

PVOD and PCH share clinical, pathological, and genetic characteristics, and treatment is the same.[27] PVOD may be associated with systemic sclerosis, HIV infection, or drugs. The familial form is caused by mutations in the biallelic EIF2AK4 gene.[28]

Diagnosis is established by clinical criteria, physical examination, bronchoscopy, and radiological tests [I, C], or identification of the EIF2AK4 gene mutation [I, B].

Vasodilators can cause pulmonary edema in PVOD/PCH. Lung transplantation is the treatment of choice, so patients should be referred to a lung transplantation unit after diagnosis [I, C].

Special Situations

Pregnancy and birth control: due to the high risk of mortality, patients with PAH should avoid pregnancy [I, C]. The combined use of 2 contraceptive methods is advisable. Progestins are preferable to estrogens. If pregnancy occurs, patients should be informed of the risk and termination should be proposed. Patients who decide to take the risk and continue the pregnancy should be monitored closely in a center with expertise in PH and high-risk pregnancies.

Surgery: surgery confers a high risk of morbidity and mortality, especially if it is unscheduled,[29] and should be performed in PH reference centers. Epidural anesthesia is preferable to general anesthesia.[29]

Right heart failure: diuretics provide symptomatic benefits. In situations requiring ICU admission, the patient's water balance must be optimized with intravenous diuretics, right ventricular overload must be minimized (generally with intravenous prostanoids), cardiac output must be optimized (preferably with dobutamine). Intubation, which frequently produces hemodynamic collapse, should be avoided. Extracorporeal membrane oxygenation (ECMO) and other devices should be considered in selected patients.[30]

Pulmonary Hypertension due to Left Heart Disease

PH associated with left heart disease is classified as post-capillary. Two types have been identified: Isolated post-capillary PH and combined pre-capillary and post-capillary PH, depending

Table 9
Hemodynamic Classification of Post-capillary Pulmonary Hypertension.

Definition	Characteristics
Post-capillary PH	mPAP ≥25 mmHg PAWP >15 mmHg
Isolated post-capillary PH	DPG <7 mmHg and/or PVR ≤3 WU
Combined post-capillary and pre-capillary PH	DPG ≥7 mmHg and/or PVR >3 WU

DPG: diastolic pressure gradient (diastolic PAP–PAWP); mPAP: mean pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; WU: Wood units (mmHg/L/min).

Table 10
Data Indicative of Heart Failure With Preserved Ejection Fraction.

Age >65 years
Cardiovascular risk factors: diabetes mellitus, dyslipidemia, or systemic hypertension
Coronary disease
Atrial fibrillation
Echocardiography: left atrium more dilated than right, left ventricular hypertrophy, interatrial septum bulging into the right atrium, diastolic dysfunction in mitral flow Doppler
ECG: presence of left ventricular hypertrophy and Q waves

on diastolic pressure gradient values and pulmonary vascular resistance (Table 9).

Differential diagnosis between PAH and group 2 PH can be complex, particularly in patients with PH and heart failure with preserved ejection fraction. Attention will be given to the characteristics indicated in Table 10.[31]

The approach focuses on optimizing heart failure treatment [I, B]. Patients with severe combined post-capillary and pre-capillary PH should be referred to expert centers for inclusion in clinical trials and/or individualized treatment [IIa, C]. The use of drugs indicated for PAH is not recommended [III, C].

Table 11
Hemodynamic Classification of Pulmonary Hypertension Associated With Respiratory Diseases.

Terminology	Hemodynamic characteristics
COPD/IPF/CPFE without PH	mPAP <25 mmHg
COPD/IPF/CPFE with PH	mPAP ≥25 mmHg
COPD/IPF/CPFE with severe PH	mPAP >35 mmHg or mPAP ≥25 mmHg in the presence of low cardiac output (CI <2.5 L/min, not explained by other causes)

CPFE: combination of pulmonary fibrosis and emphysema; CI: cardiac index; COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; mPAP: mean pulmonary arterial pressure; PH: pulmonary hypertension.

Pulmonary Hypertension due to Respiratory Disease

Respiratory diseases most commonly associated with PH are COPD, interstitial lung diseases, and the combination of pulmonary fibrosis and emphysema. Table 11 shows the hemodynamic classification of PH in this group. PH is usually mild or moderate.[32] Severe PH is most often seen in the combination of pulmonary fibrosis and emphysema (CPFE) and is often associated with a disproportionately reduced carbon dioxide diffusing capacity and low $PaCO_2$.[33]

TTE is the examination of choice for the detection of PH [I, C], although its accuracy in patients with advanced respiratory disease is low. This procedure is indicated if significant PH is suspected or to rule out left heart disease.

The definitive diagnosis of PH is established with RHC. Indications include: 1) correct diagnosis or exclusion of PH in candidates for surgery (transplantation, lung volume reduction); 2) suspected concomitant PAH or chronic thromboembolic pulmonary

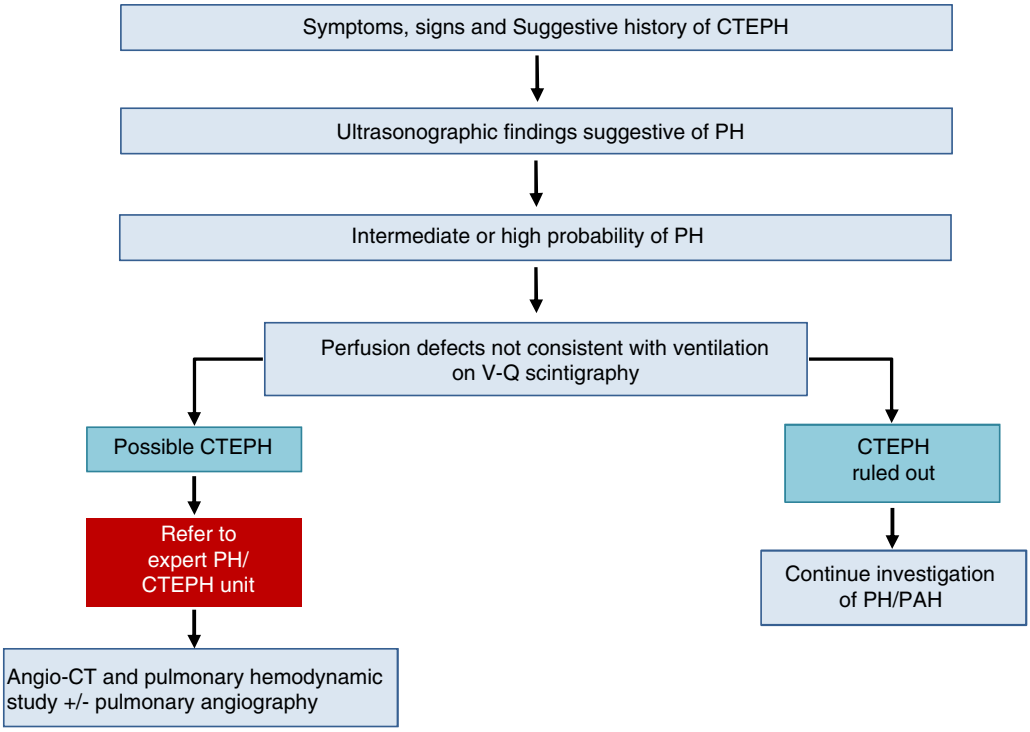

Fig. 3. Diagnostic algorithm for pulmonary hypertension.
CTEPH: chronic thromboembolic pulmonary hypertension; CT: computed tomography; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; V-Q: ventilation–perfusion.

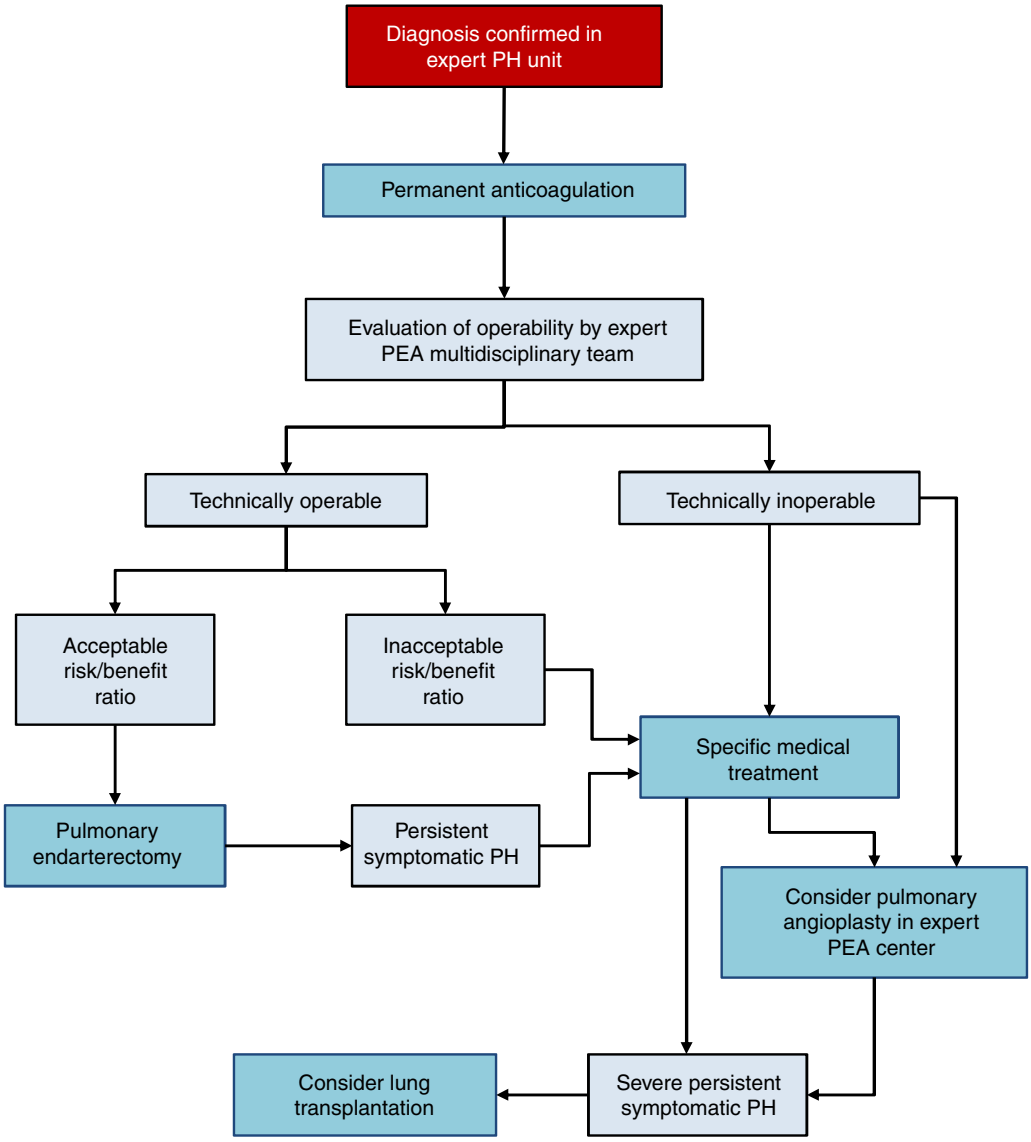

Fig. 4. Therapeutic algorithm for chronic thromboembolic pulmonary hypertension. PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

hypertension (CTEPH); 3) repeated episodes of right heart failure, and 4) inconclusive TTE in cases with high suspicion of PH.[34]

The treatment of choice in patients with COPD and hypoxemic PH is continuous home oxygen therapy [I, C]. The role of oxygen therapy is less clear in interstitial disease.

Conventional vasodilators or specific PAH drugs are not recommended in COPD patients with mild-moderate PH [III, C].[2,35] The use of ambrisentan and riociguat is contraindicated in idiopathic pulmonary fibrosis [III, A]. Patients with respiratory disease and severe PH should be referred for individualized treatment in a hospital specializing in both conditions [I, C].

Chronic Thromboembolic Pulmonary Hypertension

A diagnosis of CTEPH is established by the presence of pulmonary thrombosis and pre-capillary PH, after more than 3 months of appropriate anticoagulation.

The diagnostic algorithm for CTEPH (Fig. 3) has 2 components: hemodynamic diagnosis by RHC and localization of thrombotic lesions using imaging techniques (angio-CT and selective pulmonary digital subtraction angiography).

There are 3 treatment options in CTEPH (Fig. 4):

1. Surgery

Pulmonary endarterectomy (PEA) is the treatment of choice [I, C]. This intervention can achieve cure of CTEPH and is appropriate in more than 60% of cases. All patients diagnosed with CTEPH should be evaluated for possible PEA by a multidisciplinary team that includes a specialized surgeon in a hospital with experience in this type of surgery [I, C]. There are 2 accredited centers in Spain.[36–38]

2. Medical intervention

Patients with CTEPH should receive chronic anticoagulation, even after PEA [I, C]. Vitamin K antagonists are recommended, since there is no evidence to support the use of the new oral anticoagulants. Currently, the only drug specifically indicated for CTEPH is riociguat[39] [I, B]. Beneficial effects have been demonstrated with macitentan,[40] and to some extent with bosentan.[41] Pharmacological treatment is indicated in patients in whom surgery has been ruled out by an expert multidisciplinary committee in PEA and if PH persists after PEA [I, B].

Table 12
Recommendations for Expert Pulmonary Hypertension Units.

Multidisciplinary team of professionals [I, C]
Monitoring >50 patients with PAH and CTEPH (ideally >200) [IIa, C]
Receive >24 new cases per year with a diagnosis of PAH and CTEPH [IIa, C]
Perform >20 right heart catheterizations with vasodilator test every year [IIa, C]

CTEPH: chronic thromboembolic pulmonary hypertension; PAH: pulmonary arterial hypertension.
[Class of recommendation, level of evidence].

3. Pulmonary angioplasty

Pulmonary balloon angioplasty is a new procedure that has provided good outcomes in patients with obstructive lesions that cannot be accessed with PEA,[42–44] although the available evidence is still scant.[45] This procedure should only be performed in hospitals with extensive experience in CTEPH, after PEA has been ruled out.[2]

Pulmonary Hypertension With Unclear or Multifactorial Mechanisms

This group includes various etiological processes: hematologic diseases, systemic diseases, metabolic disorders, and a miscellaneous group of disorders (Table 2). Diagnosis is difficult, so management in hospitals with experience in PH is advisable. Currently there is no specific treatment for this group.

Healthcare Organization

Primary forms of PH (groups 1, 4, and 5) (Table 2) are rare serious diseases that require complex procedures for diagnosis and treatment. The broad consensus is that patients with diseases of these characteristics should be seen in specialized referral units with experience in the disease.[2,46] In 2008, the Spanish Society of Pulmonology and Thoracic Surgery and the Spanish Society of Cardiology prepared a consensus document in which they proposed a healthcare organization for the care of PH patients in Spain based on expert PH units that interact in a network with hospitals at a local level.[46] The criteria that expert PH units must meet, as established in the clinical guidelines of the European Society of Cardiology-European Respiratory Society,[2] are shown in Table 12. Three CSURs (centers, services or units of reference) for complex PH cases, appointed by the Ministry of Health, have been operating in Spain since 2015.

Given the organizational structure of the Spanish healthcare system, care in the area of PH must be set up a network of networks, with expert PH units on an autonomous community level, which interact with associated sites within the autonomous community itself. CSURs, which can deliver PEA programs and care in more complex patients and situations, must operate on a national level.

Expert PH units must set up protocols for consultation circuits and referral for specific diseases and clinical situations: CTEPH (PEA, pulmonary angioplasty), lung transplantation, portopulmonary hypertension, congenital heart disease, connective tissue diseases, genetic studies, elective surgery and care of the pregnant patient.

Conflict of Interests

Dr. Barberà has received fees from Actelion, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer, and has received funding from Actelion, Bayer, GlaxoSmithKline and Pfizer, not related with this publication. Dr. Blanco has received fees from Merck Sharp & Dohme, not related with this publication. Dr. Otero Candelera has received fees from Actelion, Bayer, Rovi, Leo Pharma, and Merck Sharp & Dohme, and has received funding from Bayer and Leo Pharma, not related with this publication. Dr. Lopez-Reyes has received fees from Actelion, and funding from GlaxoSmithKline, Ferrer, and Actelion, not related with this publication. Dr. Otero has received fees from Actelion, Bayer, Glaxo-SmithKline, and Ferrer, not related with this publication. Dr. Pérez-Peñate has received fees from Actelion, Bayer, and Merck Sharp & Dohme, not related with this publication. Dr. Sala declares no conflict of interests. Dr. Escribiano has received fees from Actelion, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme, and has received funding from Actelion, Bayer, GlaxoSmithKline and Ferrer, not related with this publication.

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