

## 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)

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Substantial progress in the diagnosis and treatment of patients with pulmonary hypertension in recent years has led to significant improvement in survival. Evidence-based clinical practice guidelines issued by scientific societies reflect these new developments. However, certain clinically relevant issues have not been covered in consensus guidelines because of the lack of conclusive scientific evidence. Therefore, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Cardiology (SEC) have promoted the present consensus statement in order to define national standards of care in the evaluation and management of pulmonary hypertension in its various forms, as well as to outline a clinical pathway and the basic principles for organizing health care in this clinical setting, with special emphasis on the requirements for and functions of specialized referral units. To prepare the statement, SEPAR and SEC formed a task force composed of national experts in various aspects of pulmonary hypertension. The resulting consensus is based on international clinical guidelines, a review of available scientific evidence, and panel discussion among the task force members. The final statement, approved by all participants, underwent external review.

**Key words:** *Pulmonary hypertension: diagnosis and therapy. Antihypertensive agents. Lung transplantation. Clinical practice guidelines.*

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Estándares asistenciales en hipertensión pulmonar  
Documento de consenso elaborado por la Sociedad Española de Neurología y Cirugía Torácica (SEPAR) y la Sociedad Española de Cardiología (SEC)

En los últimos años se han producido importantes avances en el diagnóstico y tratamiento de la hipertensión pulmonar que han logrado una mejoría significativa en la supervivencia de esta enfermedad. Estas innovaciones se han recogido en guías de práctica clínica basadas en la evidencia elaboradas por las sociedades científicas. Sin embargo, no se incluyen en ellas, por falta de evidencia científica concluyente, algunos aspectos que inciden en la práctica asistencial. Conscientes de ello, la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) y la Sociedad Española de Cardiología (SEC) han promovido la elaboración de un documento de consenso para definir en nuestro medio los estándares de calidad adecuados para el diagnóstico y tratamiento de la hipertensión pulmonar en sus diversas formas de presentación, así como la vía clínica y las directrices básicas de la organización asistencial del cuidado de estos pacientes, haciendo especial hincapié en los requisitos y funciones de las unidades de referencia. Para su redacción la SEPAR y la SEC designaron a un grupo de trabajo formado por expertos en los distintos aspectos de la enfermedad. Para la elaboración del documento se han utilizado las guías clínicas internacionales existentes, la revisión de la evidencia científica disponible y el debate en panel entre los expertos. El documento final, aprobado por todos los participantes, ha sido evaluado por revisores externos.

**Palabras clave:** *Hipertensión pulmonar, diagnóstico y tratamiento. Agentes antihipertensivos. Trasplante pulmonar. Guías de práctica clínica.*

## 1. Introduction

Recent years have seen substantial progress in the clinical management of pulmonary hypertension, particularly with the advent of new treatments leading to significant

improvement in survival for patients with the most severe forms of this disease. The innovations have been reflected in clinical practice guidelines issued by international scientific societies<sup>1-4</sup>; these guidelines state the current standard for the diagnosis and treatment of pulmonary hypertension. Certain clinically relevant issues have not been covered in these statements, however, because of a paucity of conclusive scientific evidence. In addition, the appropriate diagnosis and treatment of pulmonary hypertension, particularly in its most severe forms, require specialized techniques and personnel with solid experience with the disease. To meet health care needs in Spain, we must have at our disposal a structure that can provide a sufficient standard of care for patients with pulmonary hypertension to ensure satisfactory management of their disease.

Cognizant of this, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Cardiology (SEC) have promoted the present consensus statement in order to define national standards of care in the diagnosis and management of pulmonary hypertension in its various forms, as well as to outline the clinical pathway for patients and provide principles for organizing their health care, consistent with the necessary level of specialization and considering the prevalence of this disease.

SEPAR and SEC were charged with coordinating the preparation of this statement. In turn, these societies each requested that an equal number of specialists in various aspects of the disease form a working group. The present statement was based on current international guidelines, especially those of the European Society of Cardiology,<sup>1</sup> a review of available scientific evidence, and debate among members of the expert panel. The statement was drafted by the coordinators and reviewed by all members of the working group on numerous occasions in order to come to an agreement on a final version. Two external reviewers then assessed the document, after which it was approved by the scientific committees and boards of SEPAR and SEC.

## 2. Definition and Classifications

Pulmonary hypertension refers to an abnormal elevation of pressure in the pulmonary artery. By consensus, pulmonary hypertension is considered to be present when the mean pulmonary artery pressure (PAP) is 25 mm Hg or more at rest or 30 mm Hg during exercise.

Such hypertension may develop in the context of various clinical processes or diseases. According to current convention, these types of hypertension are grouped into 5 classes or categories<sup>1</sup>: I, pulmonary arterial hypertension (PAH); II, pulmonary hypertension associated with left heart diseases; III, pulmonary hypertension associated with respiratory disease and/or hypoxia; IV, pulmonary hypertension due to chronic thrombotic and/or embolic disease; and V, a group of miscellaneous forms. Table 1 lists the diseases and clinical processes included in each category of this essentially clinical classification system. Processes and diseases are grouped in categories that share similar pathophysiologic mechanisms, clinical presentations, and therapeutic options.

TABLE 1  
Clinical Classification of Pulmonary Hypertension

I. Pulmonary arterial hypertension
Idiopathic
Familial
Associated with:
Connective tissue disease
Congenital systemic to pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
II. Pulmonary hypertension associated with left heart diseases
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
III. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
IV. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
V. Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

The groups associated with the poorest prognosis, and which therefore require prompt diagnostic and therapeutic decision-making, are PAH and pulmonary hypertension due to chronic thrombotic and/or embolic disease. These 2 categories are defined by additional criteria, namely a pulmonary artery occlusion pressure (PAOP) of less than 16 mm Hg and pulmonary vascular resistance greater than 3 mm Hg·L<sup>-1</sup>·min<sup>-1</sup> (Wood units) or 240 dyne·s·cm<sup>-5</sup>.

## 3. Diagnostic Process

The diagnosis of pulmonary hypertension is the fruit of a gradual process of detection, classification, and assessment. Four diagnostic stages can be defined: I, suspicion; II, detection; III, identification of class; and IV, evaluation and diagnosis of type (Table 2).

Suspicion of pulmonary hypertension is eminently clinical, based on symptoms, the presence of risk factors, the findings of physical examination or simple chest radiographs or an electrocardiogram.

The main tool for detecting pulmonary hypertension is transthoracic echocardiography (TTE), which should therefore always be ordered when suspicion is present. TTE estimates pulmonary artery systolic pressure (PASP) based on regurgitant tricuspid flow velocity and provides information on possible cardiac causes for pulmonary hypertension as well as its consequences on right ventricular size and function. Pulmonary hypertension is assumed when the velocity of the regurgitating tricuspid jet exceeds  $2.8 \text{ m}\cdot\text{s}^{-1}$ , a value that is approximately equivalent to a PASP greater than 36 mm Hg. It must be remembered, however, that the value of that threshold naturally increases with age.<sup>5</sup> TTE detects possible pulmonary hypertension, but does not provide a diagnosis, which can only be based on a study of pulmonary hemodynamics by means of right heart catheterization. Given the possibility of a false negative when pulmonary hypertension is clearly suggested by TTE in the absence of elevated PASP, it is advisable to proceed to evaluate pulmonary hemodynamics in order to rule out the diagnosis. Parameters to be measured by TTE are properly standardized (Table 3).

Once a potential case of pulmonary hypertension has been detected, the next step is to identify class according to the categories in Table 1, by means of the tests listed in Table 2.

After ultrasound detection of pulmonary hypertension and performance of the indicated tests, patients with PAH, with pulmonary hypertension due to chronic thrombotic and/or embolic disease, and with respiratory disease and PASP elevation that is inconsistent with the severity of their underlying process should be referred to a specialized unit for the remainder of the diagnostic process.

A diagnosis of pulmonary hypertension is completed by means of *a*) a study of pulmonary hemodynamics, *b*) the evaluation of exercise capacity, and *c*) tests specific to the type of pulmonary hypertension present. Right heart catheterization is the gold standard procedure for the study of pulmonary hemodynamics in the diagnostic process. Findings facilitate an assessment of severity and contribute to prognosis. Catheterization is indicated for all patients with PAH or pulmonary hypertension due to chronic thrombotic and/or embolic disease (classes I and IV, respectively); it is justified in other circumstances if its findings would lead to a change in the assessment of the patient's clinical status or to a change in treatment. For patients with a PASP less than 50 mm Hg estimated by TTE, the decision of whether or not to perform right heart catheterization will be individualized, based on age, the grounds for clinical suspicion, and concomitant disease.

The diagnostic assessment of hemodynamic function should be accompanied by a test of acute vasodilator response using a recommended agent (intravenous epoprostenol adenosine or inhaled nitric oxide). The findings of vasoreactivity testing have important implications for treatment and prognosis. A test is considered positive when it produces a decrease of at least 10 mm Hg in mean PAP and a final pressure of 40 mm Hg or less without an accompanying decrease in cardiac output.

Both the study of pulmonary hemodynamics and the test of vasoreactivity must be carried out by experienced personnel in units with the proper equipment.

TABLE 2  
Diagnostic Process for Pulmonary Hypertension

Stage	Tests and Observations
Suspicion	Symptoms, physical examination, chest radiograph, electrocardiogram
Detection	TTE
Identification of class and type	TTE (left heart valvular or myocardial disease, congenital heart disease) TTE with agitated saline (intra- or extracardiac shunt) Respiratory function tests: spirometry, static lung volumes, carbon monoxide diffusing capacity, and arterial blood gases Ventilation-perfusion lung scan (scintigraphy) Routine blood tests plus tests for: Thyroid function Liver function Immunology screening (antinuclear, anti-DNA, anticentromere, anticardiolipin, and anti-U1-RNP antibodies) HIV, hepatitis B and C serology Optional tests High-resolution chest CT scan Spiral CT angiography Abdominal ultrasound Sleep studies Selective pulmonary arteriography, in the case of pulmonary hypertension due to chronic thrombotic and/or embolic disease Transesophageal echocardiography
Evaluation and diagnosis	Hemodynamics: Pulmonary artery catheterization Acute vasodilator testing Exercise capacity: Six-minute walk test Cardiopulmonary stress test (optional)

Abbreviations: CT, computed tomography; TTE, transthoracic echocardiography.

The evaluation of a patient with pulmonary hypertension is completed with an assessment of severity. For that purpose, the following aspects are taken into account: *a*) functional class on the New York Heart

TABLE 3  
Echocardiographic Variables Required for the Diagnosis of Pulmonary Hypertension

Screening and detection
Right ventricular and atrial dimensions and function
Left ventricular and atrial dimensions and function
Valve abnormalities (grade and severity of tricuspid and pulmonary regurgitation)
Left ventricular filling characteristics (diastolic function of the left ventricle)
Estimate of pulmonary artery systolic pressure
Inferior vena cava dimensions
Pericardial effusion, presence and size
Evaluation of class and type of pulmonary hypertension
Agitated saline test
Left ventricular eccentricity index
Right ventricular (Tei) index

Association (NYHA) scale, as modified by the World Health Organization,<sup>1</sup> b) exercise tolerance, c) electrocardiographic and hemodynamic findings, and d) blood tests. Exercise tolerance is usually assessed with a 6-minute walk test, which should be carried out according to current recommendations.<sup>6</sup> The results should be interpreted in accordance with reference values that consider the patient's sex, age, and height.<sup>7</sup> Patients in NYHA functional class I or II may have a normal walk test result. In that case, a cardiopulmonary stress test might provide more precise information regarding exercise tolerance and limiting factors.

### 3.1. Special Situations

– For a diagnosis of familial PAH, if there is a family history of pulmonary hypertension, the possibility of a mutation in the bone morphogenetic protein receptor 2 gene *BMPR2* should be explored in the diagnosed patient (the index case). If the mutation is found, other members of the family should be tested in order to facilitate the early detection of asymptomatic pulmonary hypertension.

– The diagnosis of pulmonary hypertension due to chronic thrombotic and/or embolic disease is based on the presence of thrombotic phenomena and pulmonary hypertension after more than 3 months of appropriate anticoagulant therapy. The proximal or distal location of thrombotic lesions must be established, for which purpose the gold standard procedure is selective pulmonary angiography. Spiral computed tomography (CT) angiography carried out with the latest generation equipment also provides high-quality images, although this technique is currently considered a complement to conventional angiography rather than a substitute for it. The evaluation of patients with pulmonary hypertension due to chronic thrombotic and/or embolic disease should take place in centers that specialize in the disease, preferably with experience in pulmonary thromboendarterectomy.

– In patients with pulmonary hypertension associated with left heart disease, echocardiographic detection of an elevated PASP does not by itself constitute an indication for hemodynamic evaluation. Right heart catheterization should be performed when the diagnosis is uncertain as to whether the hypertension detected by ultrasound is precapillary (in PAH) or postcapillary (pulmonary hypertension associated with left heart disease) in patients with generally normal systolic function and only diastolic or left ventricular dysfunction.

– Hemodynamic assessment is also unnecessary in patients with pulmonary hypertension associated with respiratory disease, unless the TTE-estimated PASP is disproportionately high (>55 mm Hg) in relation to the severity of the respiratory condition and it is believed that pulmonary hypertension might be a concomitant disease and possibly respond to disease-specific treatment.

– Polysomnography to screen for sleep apnea syndrome need not be performed in all patients with pulmonary hypertension, unless there is clinical suspicion.

## 4. Treatment

### 4.1. Pulmonary Arterial Hypertension

#### 4.1.1. General Measures

General measures involve strategies intended to reduce the harmful effects that some circumstances and external agents have on the patient with pulmonary hypertension.

– Physical exercise can increase mean PAP, so activity that can produce severe symptoms (syncope or presyncope) should be avoided. Progressive, light aerobic exercise 4 to 5 days per week is advisable.

– Supplemental oxygen should be used during commercial flights of more than 2 hours or if respiratory failure is present.

– Pregnancy causes hormonal and hemodynamic changes that can be very poorly tolerated. Maternal mortality is high at 30% to 50% in this situation, particularly in the early postpartum period. Contraception is therefore essential. Combined hormonal contraceptives, however, are not to be recommended because of their possible prothrombotic effect. Barrier methods or estrogen-free hormonal contraceptives may be employed. Surgical sterilization for women or intrauterine devices require follow-up and anesthesia administered by a specialist because of the likelihood of life-threatening complications (vasovagal reactions). In case of pregnancy, first-trimester abortion is recommended.

#### 4.1.2. Medical Treatment

##### 4.1.2.1. Nonspecific Drugs

– *Continuous home oxygen therapy.* Oxygen therapy should be prescribed for patients with respiratory failure with the purpose of maintaining arterial oxygen saturation above 90%.

– *Diuretics.* Diuretic treatment is indicated to reduce the signs and symptoms of right heart failure. Spironolactone is particularly recommended.

– *Digitalis.* This drug should be used in cases of clinically evident right ventricular failure or atrial fibrillation.

– *Oral anticoagulants.* Anticoagulation is recommended for patients with idiopathic PAH and associated forms, with the exception of portopulmonary hypertension with esophageal varices. The use of anticoagulant therapy in Eisenmenger syndrome is debated. An international normalized ratio (INR) between 1.5 and 2.5 should be maintained.

– *Calcium channel blockers (vasodilators).* Chronic treatment with high doses of calcium channel blockers improves survival in patients with a significant positive response in an acute vasodilator test. The most frequently used drugs are diltiazem and nifedipine, which have been shown to be effective at relatively high doses of 240-720 mg/d for diltiazem and 120-240 mg/d for nifedipine. The efficacy of calcium channel blockers must be assessed 3 to 6 months after starting treatment. They are considered effective if the patients are in functional class I or II and PASP approaches normal values. If those targets are not achieved, specific drug therapy should be initiated.

TABLE 4  
Disease-Specific Drugs for Pulmonary Hypertension

Drug	Route	Dosage	Approval	Monthly Cost	Warnings and Side Effects
Epoprostenol	Intravenous	Initial: 2 ng/kg/min Maintenance: 20-40 ng/kg/min	USA; Europe, including Spain	€22 800 <sup>a</sup>	Septic central venous catheter Rebound Headache, lower jaw pain, diarrhea, exanthems
Iloprost	Inhaled	Maintenance: 15-45 µg/24 h <sup>b</sup>	USA; Europe, including Spain	€4584	Dry cough Headache
Treprostinil	Subcutaneous	Initial: 2 ng/kg/min Maintenance: 20-80 ng/kg/min	USA; Europe, not including Spain		Local pain and inflammation Headache, lower jaw pain, diarrhea, exanthems
Bosentan	Oral	Initial: 62.5 mg/12 h Maintenance: 125 mg/12 h	USA; Europe, including Spain	€2485	Elevated liver transaminase concentration requiring monthly monitoring
Sitaxsentan	Oral	Maintenance: 100 mg/24 h	Europe, including Spain	€2485	Mild anemia
Ambrisentan	Oral	Maintenance: 5-10 mg/24 h	USA		Peripheral edema
Sildenafil	Oral	Initial: 20 mg/8 h Maintenance: 20-80 mg/8 h	USA; Europe, including Spain	€462	Headache, dyspepsia Do not prescribe with nitrates.

<sup>a</sup>Dosage for a person weighing 65 kg: 30 ng·kg<sup>-1</sup>·min<sup>-1</sup>

<sup>b</sup>Dose sprayed into the mouth with a nebulizer.

The long-term usefulness of calcium channel blockers is less certain in patients with PAH associated with collagenosis or HIV infection who have had a positive reaction in an acute vasodilator challenge test. Calcium channel blockers are not indicated in Eisenmenger syndrome or portopulmonary hypertension.

#### 4.1.2.2. Disease-Specific (Targeted) Drug Therapy (Table 4)

##### 4.1.2.2.1. Prostanoid Therapy

– Epoprostenol is the drug for which the most clinical experience has been reported. The efficacy of this drug in functional class IV patients with PAH has been most clearly demonstrated and it has the strongest evidence indicating that it increases survival. Epoprostenol is administered by continuous infusion through a permanent central venous catheter, with all the implications of such a technique. If therapy is interrupted, a rebound effect with serious complications may ensue, and infusion should therefore be reinstated as soon as possible.

– Iloprost is an analog of prostacyclin that has a serum half-life of 20 to 25 minutes and must be inhaled in 6 to 9 puffs daily. Iloprost may also be administered intravenously, although experience with that route is limited.

– Treprostinil is a prostacyclin analog with a serum longer half-life of 2 to 3 hours, making subcutaneous administration possible. The main side effect is pain and local inflammation at the injection site, necessitating

specific measures and possibly requiring a change in treatment. Treprostinil may also be administered intravenously, although experience with this form of delivery is limited. Clinical trials are currently under way to test the efficacy of inhaled and oral forms of administration.

##### 4.1.2.2.2. Endothelin Receptor Antagonists

– Bosentan is a dual A- and B-receptor antagonist of endothelin-1 that is administered orally. It may cause liver toxicity (transaminase concentrations more than 3 times the upper limit of normal) that is reversible in 8% of the patients, and monthly liver function testing is therefore necessary. Bosentan has a slight teratogenic effect and is contraindicated in case of pregnancy. It also interacts with oral contraceptives, limiting their efficacy, and with glibenclamide, increasing the risk of liver toxicity.

– Sitaxsentan, a selective antagonist of endothelin-1 receptor A, was recently approved in Spain and as yet there are few reports of experience with it.

– Ambrisentan, a selective antagonist of endothelin-1 receptor A, was approved by the US Food and Drug Administration recently (June 2007) following completion of controlled clinical trials.

##### 4.1.2.2.3. Phosphodiesterase-5 Inhibitors

– Sildenafil is a phosphodiesterase-5 inhibitor that is administered orally at a recommended dose of 20 mg every

TABLE 5  
**Drugs Specific to the Treatment of Pulmonary Hypertension**

	Prostanoids		
	Epoprostenol	Treprostinil	Iloprost
Indicated	<i>FC III-IV</i> PAH; idiopathic, familial, CTD, drugs or toxins	<i>FC III</i> PAH; idiopathic, familial, CTD, drugs or toxins	<i>FC III</i> PAH; idiopathic, familial, CTD, drugs or toxins
Acceptable	<i>FC III-IV</i> PAH: PH with HIV, congenital heart disease PH due to chronic thrombotic and/or embolic disease unrelated to surgery, or residual postoperative PH  Portopulmonary hypertension in patients awaiting a liver transplant	<i>FC III</i> PAH: PH with HIV, congenital heart disease PH due to chronic thrombotic and/or embolic disease unrelated to surgery, or residual postoperative PH  <i>Any PH in FC IV</i> Portopulmonary hypertension	<i>FC III</i> PAH: PH with HIV, congenital heart disease PH due to chronic thrombotic and/or embolic disease unrelated to surgery, or residual postoperative PH  <i>Any PH in FC IV</i> Portopulmonary hypertension
Experimental	PH with veno-occlusive disease or pulmonary capillary hemangiomatosis <sup>b</sup>	PH with veno-occlusive disease or pulmonary capillary hemangiomatosis <sup>b</sup>	PH with veno-occlusive disease or pulmonary capillary hemangiomatosis <sup>b</sup>
Not recommended	<i>Any PH in FC I-II</i> PH associated with left heart disease PH associated with respiratory disease	<i>Any PH in FC I-II</i> PH associated with left heart disease PH associated with respiratory disease	<i>Any PH in FC I-II</i> PH associated with left heart disease PH associated with respiratory disease

	Endothelin-1 Receptor Antagonists		Phosphodiesterase-5 Inhibitors
	Bosentan	Sitaxsentan or Ambrisentan <sup>c</sup>	Sildenafil
Indicated	<i>FC III</i> PAH: idiopathic, familial, CTD, drugs or toxins, and congenital heart disease	<i>FC III</i> PAH: idiopathic, familial, CTD,	<i>FC III</i> PAH: idiopathic, familial, CTD, drugs or toxins
Acceptable	<i>FC II</i> PAH: idiopathic, familial, CTD <i>FC III</i> PAH: PH in HIV PH due to chronic thrombotic and/or embolic disease unrelated to surgery, or residual postoperative PH  Other <sup>d</sup> <i>Any HP in FC IV</i>		<i>FC II</i> PAH: idiopathic, familial, CTD <i>FC III</i> PAH: PH in HIV PH due to chronic thrombotic and/or embolic disease unrelated to surgery, or residual postoperative PH Other <sup>d</sup> <i>Any PH in FC IV</i>
Experimental	PH with veno-occlusive disease or pulmonary capillary hemangiomatosis <sup>b</sup> Portopulmonary hypertension Child A or B Disproportionate PH (mean PAP >40 mm Hg) in pulmonary fibrosis and COPD PH associated with left heart disease, feasible heart transplantation, perioperative period after heart surgery		PH with veno-occlusive disease or pulmonary capillary hemangiomatosis <sup>b</sup> Portopulmonary hypertension Disproportionate PH (mean PAP >40 mm Hg) in pulmonary fibrosis PH associated with left heart disease, feasible heart transplantation, perioperative period after heart surgery
Not recommended	<i>Any PH in FC I</i> PH associated with left heart disease PH associated with respiratory disease and mean PAP <40 mm Hg Portopulmonary hypertension Child	<i>Any PH in FC I</i> PH associated with left heart disease PH associated with respiratory disease	<i>Any PH in FC I</i> PH associated with respiratory disease and mean PAP <40 mm Hg

Abbreviations: COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; FC, functional class of the New York Heart Association-World Health Organization; PH, pulmonary hypertension; PAH pulmonary arterial hypertension; PAP, pulmonary artery pressure.  
<sup>a</sup>PH in hemolytic anemia, myeloproliferative syndromes, splenectomy, Rendu-Osler disease, Gaucher disease.  
<sup>b</sup>High risk for acute pulmonary edema. Undertake this procedure only in hospitals with experience.  
<sup>c</sup>Recently approved by the US Food and Drug Administration (June 15, 2007); indications have not yet been set in Europe.

TABLE 6  
**Risk Factors for an Unfavorable Outcome of Therapy for Pulmonary Hypertension**

Low	Indicator of Risk	High
No	Signs of right heart failure	Yes
Stability	Progression	Rapid
>500 m	Distance walked on the 6-minute walk test	<350 m
Normal or near-normal value	Natriuretic peptides	Very high value
Mild right ventricular dysfunction	Cardiac ultrasound	Pericardial effusion, severe right ventricular dysfunction
Mild right ventricular dysfunction	Pulmonary hemodynamics	Mean RAP>12 mm Hg CI<2 L min <sup>-1</sup> .m <sup>-2</sup> SvO <sub>2</sub> <63%

Abbreviations: CI, cardiac index; RAP, right atrial pressure; SvO<sub>2</sub>, mixed venous oxygen saturation in the pulmonary artery.

8 hours, although doses up to 4-fold higher have been given. Sildenafil interacts with some antiretroviral drugs and dosages must therefore be tailored when administered concomitantly. It may never be used in association with nitrates because of the risk of severe hypotension.

– Tadalafil is a more potent phosphodiesterase-5 inhibitor that is currently under investigation in this clinical context in a controlled clinical trial nearing completion.

#### 4.1.2.3. Indications and Usage Recommendations (Table 5)

The indications for monotherapy with drugs that specifically target pulmonary hypertension and recommendations for other uses have been divided into 4 categories according to the level of supporting evidence available, the authorization by regulatory agencies,<sup>8</sup> recommendations in clinical guidelines<sup>1-4</sup> and the scientific literature:

1. Established indication: stipulated in current clinical guidelines and authorized by drug regulatory agencies.

2. Acceptable use: indications that are accepted by experts and that form part of routine clinical practice. Even though their efficacy has not yet been verified by controlled clinical trials, it is supported by a certain level of evidence from uncontrolled trials.

3. Experimental use: indications that have not been recognized or validated by the scientific community and which therefore must be considered experimental. It is recommended that use of a drug in this category be undertaken only by caregivers experienced with the treatment of pulmonary hypertension, preferably in the context of clinical trials or supported by registries that will allow the results to be analyzed.

4. Not recommended: unrecognized indications that have not been validated by the scientific community and that are considered inappropriate.

#### 4.1.2.4. Combined Treatment

Combined treatment with drugs from different categories may be indicated if monotherapy does not bring a patient

into low-risk status<sup>9</sup> with acceptable control of pulmonary hypertension (Table 6). Failed monotherapy is a criterion for preferential transfer to a referral unit specialized in pulmonary hypertension.

Data on the most effective combinations, dosing, and side effects are not currently available. It is therefore recommended that combined treatment be monitored carefully and within the context of such specialized referral units. Several clinical trials are presently under way to assess the efficacy and safety of various treatment combinations.

#### 4.1.3. Nonmedical Therapy

##### 4.1.3.1. Atrial Septostomy

In this treatment, a right-to-left shunt is created through the fossa ovalis as a palliative bridge to lung transplantation. Septostomy decompresses the right ventricle and increases cardiac preload, improving cardiac output and oxygen supply to the tissues in spite of a decrease in PaO<sub>2</sub>. The efficacy of this measure has only been assessed in small series. Early mortality rates following the procedure range from 5% to 13%. Atrial septostomy should be undertaken only in hospitals with experience in the technique.

Its indications are as follows:

1. Patients with severe PAH in classes III or IV, with recurrent syncope or right heart failure refractory to medical treatment.

2. Patients waiting for a lung transplant, for whom septostomy can provide a palliative bridge when no alternative is available.

Contraindications, because of high associated mortality, are imminent death, arterial oxygen saturation less than 90%, and hemoglobin concentration less than 12 g/dL.

#### 4.1.4. Lung and Heart-Lung Transplant

Transplantation may achieve normalization of pulmonary hypertension in patients with moderate or severe disease

TABLE 7  
**Lung and Heart-Lung Transplantation in Pulmonary Hypertension**

Indications for a transplant
Age <55-60 y
Absence of significant damage to extrathoracic organs
Patient receiving the maximum medical therapy (intravenous epoprostenol)
Persistence of functional class III or IV status
Distance covered in the 6-min walk test <380 m
Rapidly progressing disease
Cardiac index <2 L·min <sup>-1</sup> ·m <sup>-2</sup>
Right atrial pressure > 15 mm Hg
Indications for a heart-lung transplant
Significant left ventricular dysfunction, or dysfunction of other cardiac structures
Eisenmenger syndrome with
Severe right heart failure refractory to treatment
Oxygen saturation <60% during exercise
Complicated heart defect repair
Severe right heart failure (right ventricular ejection fraction <0.20)
Severe tricuspid regurgitation

who do not respond to medical treatment, providing significant improvement in clinical state, quality of life, and survival. Benefits have been demonstrated in uncontrolled cohort studies. The complexity of transplantation, the risk of death, and the limited benefits because of chronic rejection make this procedure the last option to consider in the therapeutic algorithm for pulmonary hypertension.

The choice of procedure (single-lung, double-lung, or heart-lung transplants) depends on the underlying disease and hemodynamic status of the patient. The preferred procedure is the double-lung transplant, whose actuarial survival rate is 50% at 5 years. Heart-lung transplantation is indicated when the heart is severely damaged and a lung transplant alone is not advisable (Table 7).

The window of opportunity is narrow and difficult to specify. Patients should be sent for evaluation by the transplant unit if they meet the general requirements,<sup>10</sup> if disease is progressing rapidly, or if the clinical course (Table 6) is unpromising and it is believed that this therapeutic option might help. In general terms, this situation occurs in PAH when the patient has been treated with intravenous epoprostenol and the response has been unsatisfactory, such that after 3 months of treatment the functional class is still III or IV and the distance walked in 6 minutes is less than 380 m.<sup>11</sup> A lung transplant is the first therapeutic choice in cases of veno-occlusive disease or pulmonary capillary hemangiomatosis, given that no medical treatment has been shown to be effective.

#### 4.1.5. Special Situations

There are forms of PAH and special circumstances that are subject to a specific approach to management and a distinct set of recommendations:

1. Congenital heart disease. Pulmonary hypertension is associated with a number of situations involving congenital heart disease, but we will refer exclusively to Eisenmenger syndrome, which is characterized by elevated pulmonary vascular resistance with reversal of left-to-right shunting. Clinical guidelines are available for this syndrome.<sup>12</sup> Although Eisenmenger syndrome patients may experience severe, prolonged functional limitation, their life expectancy is better than that of patients with other forms of pulmonary hypertension.

Eisenmenger syndrome belongs to a group of cyanotic congenital heart diseases and it should therefore be managed by professionals who specialize in that area. Pulmonary arterial vasculopathy and complications pertaining to the underlying heart disease should be taken into consideration, guided by the following general principles:

- Anticoagulation therapy is recommended for patients with atrial fibrillation, pulmonary artery thrombosis, or a history of embolism. Guided by the level of polycythemia, therapy should keep the INR between 1.5 and 2.5. Anticoagulation is not recommended if there is a history of significant hemoptysis.

- Oxygen therapy has not been reported to be beneficial.

- Bleeding is only indicated if the hematocrit exceeds 65%, in cases in which there are symptoms of hyperviscosity, or for preoperative correction of associated coagulopathy.

- Drugs that specifically target pulmonary hypertension have been used successfully in patients with Eisenmenger syndrome. However, experience is limited and published studies have been done in only small numbers of patients and for short follow-up periods. One clinical trial has been carried out with bosentan: results were good over a short follow-up period.

2. Portopulmonary hypertension. Portopulmonary hypertension is the association of pulmonary hypertension and portal hypertension with or without liver disease. It is defined hemodynamically by a mean PAP over 25 mm Hg, a PAOP of less than 15 mm Hg, and a pulmonary vascular resistance above 240 dyne·s·cm<sup>-5</sup>. Portopulmonary hypertension is associated with the highest mortality rate, attributable to hepatic disease as well as to the pulmonary hypertension itself.

The presence of pulmonary hypertension increases morbidity and mortality in liver transplantation, which is contraindicated if the patient's mean PAP exceeds 25 mm Hg.<sup>13</sup> Treatment with  $\beta$ -blockers should be withdrawn from patients with this diagnosis and if esophageal varices are present, band ligation should be carried out to prevent bleeding. Anticoagulants should not be administered.

No controlled clinical trials have been performed. The only data available come from case series with small numbers of patients and short periods of follow-up, using epoprostenol, bosentan, or sildenafil. These drugs should be prescribed by persons with experience in both pulmonary hypertension and hepatic hemodynamics, and administered in specialized units. The use of bosentan brings an added risk of possible liver toxicity and so it may be used only in patients with acceptable liver function.

#### 4.2. Pulmonary Hypertension Associated With Left Heart Disease

Pulmonary hypertension is most frequently found in the context of left heart disease, given that 30% to 40% of patients with that diagnosis also have pulmonary hypertension. Hypertension may be passive (PAOP >16 mm Hg and a transpulmonary gradient [mean PAP–PAOP] <12 mm Hg) or reactive (PAOP >16 mm Hg, transpulmonary gradient >12 mm Hg). Pulmonary hypertension, in turn, has 2 components: *a)* a reactive component that may be reversed by vasodilators, and *b)* a fixed component, the result of vascular remodeling.

Currently, pulmonary hypertension in left heart disease is treated by addressing the underlying condition, given that no specific, safe, and effective drug has been found for the chronic treatment of either passive or reactive hypertension in patients with heart failure. Medical treatment of pulmonary hypertension in this clinical setting is restricted to the perioperative period, either for the evaluation of the reversibility of pulmonary hypertension prior to surgery or heart transplantation or for the management of reversible hypertension during postoperative recovery. Drugs used for this purpose include nitric oxide, sildenafil, prostanoids, and endothelin inhibitors; within that group, nitric oxide is the one used most often after cardiac surgery.

When the utility of chronic endothelin inhibitor and epoprostenol therapy has been evaluated in controlled clinical trials with patients with heart failure, no benefit has been demonstrated.

#### 4.3. Pulmonary Hypertension Associated With Respiratory Disease or Hypoxia

Respiratory disease is also a common cause of pulmonary hypertension, although the severity is usually mild to moderate.

– *Chronic obstructive pulmonary disease (COPD)*. The currently accepted approach to managing pulmonary hypertension in COPD is to treat the underlying disease and provide continuous home oxygen therapy. A small subgroup of patients has severe hypertension (mean PAP >40 mm Hg) at a level that is unexplained by the severity of airflow limitation or hypoxia.<sup>14,15</sup> It is uncertain whether pulmonary hypertension in such cases is due to COPD or not, and it has been suggested that it may instead be a concomitant process. Calcium channel blockers to treat pulmonary hypertension are not indicated in COPD. Available information on the use of specific medical treatment is anecdotal. It should be taken into account that some specific drugs (sildenafil, prostacyclin) inhibit hypoxic pulmonary vasoconstriction and may worsen gas exchange in COPD.

– *Interstitial lung disease*. Pulmonary hypertension is usually mild in the context of interstitial lung disease, except when pulmonary fibrosis and hypertension occur alongside a connective tissue disease. Little information is available on the use of specific drugs in pulmonary hypertension associated with pulmonary fibrosis. What has been published is based only on small, open case series

of patients followed for short periods. Controlled clinical trials are currently under way.

If a patient presents connective tissue disease and concurrent, severe pulmonary hypertension and moderate pulmonary fibrosis, it is recommended to follow the treatment protocol for PAH.

– *Sleep apnea-hypopnea syndrome*. The importance of this sleep disorder as a cause of pulmonary hypertension is uncertain. Patients who have sleep apnea and proven pulmonary hypertension improve with continuous positive airway pressure. Should that not be the case, concomitant PAH should be investigated.

#### 4.4. Pulmonary Hypertension Due to Chronic Thrombotic and/or Embolic Disease

Two years after pulmonary thromboembolism, the incidence of related pulmonary hypertension is 3.8%. This form should be investigated systematically in all patients with pulmonary hypertension, whether or not they have a history of pulmonary thromboemboli. Anticoagulant treatment is indispensable (INR, 2.5–3.5).

The specific treatment for pulmonary hypertension due to chronic thrombotic and/or embolic disease is pulmonary thromboendarterectomy, provided the patient meets the following criteria:

1. Functional class III or IV on the New York Heart Association and World Health Organization scale
2. Pulmonary vascular resistance greater than 300 dyne·s·cm<sup>-5</sup>
3. Thrombi that are organized and surgically accessible (in the main, lobar, or segmental pulmonary arteries)
4. Absence of serious comorbidity

Procedural mortality ranges from 5% to 24% and is closely related to the learning curves for preoperative assessment, surgery, and postoperative care. Hospitals with the greatest volume of activity have the lowest mortality rates. Assessing the indications for surgery in a patient with pulmonary hypertension due to chronic thrombotic and/or embolic disease should be undertaken in hospitals with subspecialization in pulmonary thromboendarterectomy.

Patients with this diagnosis who are not eligible for surgical treatment are candidates for specific medical treatment (with prostanoids, bosentan, or sildenafil). Small numbers of patients have been treated successfully, though the follow-up periods have been brief. The hemodynamic improvement achieved has been clearly inferior to that which is obtained through pulmonary thromboendarterectomy, however. Medical treatment in these patients must be carried out in specialized referral units.

### 5. Clinical Follow-Up

Patients with a principal diagnosis of pulmonary hypertension (PAH or pulmonary hypertension due to chronic thrombotic and/or embolic disease) must be carefully monitored in order to: *a)* evaluate response to treatment, *b)* prevent complications, *c)* detect clinical

TABLE 8  
Clinical Follow-Up

Test or Procedure	Timing
Symptoms (functional class) Physical examination	First at 3 mo; then, every 3-6 mo
6-min walk test	First at 3 mo; then, every 6 mo
Chest radiograph, electrocardiogram	Every 6 mo
Blood tests	Every 6 mo (in patients treated with endothelin receptor antagonists, do monthly analysis of liver enzymes)
Transesophageal echocardiography	Every 6-12 mo
Pulmonary hemodynamics (right heart catheterization)	Depending on clinical course: repeat if there is deterioration or change of therapy.
Cardiopulmonary stress test	Every 6-12 mo (for patients in functional classes I or II, or walking >450 m in 6 min, or 80% of reference)
Biological markers (brain natriuretic peptides)	Not established, although testing every 6 mo is recommended

deterioration promptly, and *d*) guide therapy based on clinical course.

The response to some drugs at 3 months has been shown to predict longer-term outcome. It is therefore recommended that the patient's clinical status (functional class) and exercise tolerance (6-minute walk test) be assessed 3 months after starting treatment. Attaining functional class I or II, covering more than 380 m in 6 minutes, a peak oxygen consumption greater than 10.4 mL·kg<sup>-1</sup>·min<sup>-1</sup>, and systolic blood pressure above 120 mm Hg at the lactic acid threshold in a cardiopulmonary stress test are predictors of a good prognosis.<sup>11,16,17</sup> It is generally recommended to keep the patient in the range of a low-risk (Table 6) during follow-up. There is currently no information available from prospective studies that allow factors that can accurately predict response to treatment to be identified.

The timing of follow-up visits is dictated by the type of pulmonary hypertension, the patient's clinical status, the therapeutic regimen prescribed, and response. Table 8 shows guidelines for the follow-up scheduling.

The dimensions and functioning of the right ventricle can be determined by TTE. This information is of prognostic value and useful during follow-up. PASP bears little relation to prognosis. TTE should be repeated every 6 to 12 months.

The study of pulmonary hemodynamics 3 months after starting specific pulmonary hypertension treatment has prognostic relevance, particularly with regard to the results

for cardiac output. However, given that this procedure is invasive, it should not be undertaken systematically, but rather in accordance with the patient's clinical status, especially in cases of deterioration and when a change of treatment approach is being considered.

## 6. Organization of Care: Specialized Pulmonary Hypertension Referral Units

Pulmonary hypertension, particularly PAH or cases due to chronic thrombotic and/or embolic disease, require a high level of caregiver specialization, meaning that caseloads should be concentrated in a small number of referral units. Mentioned in all current clinical guidelines is the need to refer patients suspected of having any type of pulmonary hypertension, or particularly if pulmonary hypertension may be due to chronic thrombotic and/or embolic disease.<sup>13</sup> The reasons why specialized referral units must be created in Spain at this time are as follows:

1. The prevalence of pulmonary hypertension is not high. PAH occurs at a rate of 15 cases per million inhabitants<sup>18</sup> and may certainly be termed a rare disease: Spain is estimated to have between 600 and 800 cases.

2. PAH and pulmonary hypertension due to chronic thrombotic and/or embolic disease are entities with high associated mortality. Three-year survival for the most prevalent form, idiopathic PAH, is 47% without treatment but rises to nearly 70% if treated with the latest generation of drugs.

3. Appropriate care of these patients demands complicated diagnostic and therapeutic procedures that are available only in specialized centers. For the necessarily high level of specialization to be present, there must be experience, which can only be achieved and maintained if there is a certain volume of activity.

4. The disease-specific drugs available at this time are very costly. The price of monotherapy ranges from €460 to €23 000 per month (Table 4) and chronic treatment is necessary. Therefore, the optimum cost-effectiveness ratio is served if the decision to treat is well founded and therapy is carefully monitored.

5. The concentration of cases in specialized referral units should make it possible for there to be a critical number of patients so that multicenter clinical trials can be carried out. In that way, patients can obtain access to the most effective and/or safest drugs even before they become available on the market. Likewise, the health system thus benefits from external funding for very costly treatments.

### 6.1. Characteristics a Referral Unit Must Have

1. Staff. The following personnel would be necessary:

– At least 2 specialists (in respiratory medicine or cardiology) interested in the disease and with demonstrated professional experience should be assigned to cover patient care. One of them should be the director or coordinator of the unit and take responsibility for it.

– At least 1 registered nurse should be exclusively assigned to the unit. The nurse should have experience with the disease and the various treatments used.

– Administrative support staff will be needed to organize patient care.

The care of patients with pulmonary hypertension is highly multidisciplinary. The unit should therefore act in concert with other specialists and departments in the hospital according to diagnostic and therapeutic requirements.

2. Caseload. Given the manner in which health care in Spain is organized, a pulmonary hypertension unit should expect to handle at least 5 new cases of PAH per year and follow patients for at least 3 years. A unit will be actively managing at least 30 patients at a time.

3. Experience and quality of health care. Specialized referral units should have documented clinical experience in the main types of pulmonary hypertension—idiopathic PAH or PAH associated with HIV infection or connective tissue disease, and pulmonary hypertension due to chronic thrombotic and/or embolic disease. Also important is experience with the various drug delivery systems, particularly continuous intravenous infusion. The specialized unit's staff should hold clinical review sessions regularly to discuss patient progress. Certain outcomes should be designated as markers of success, specifically survival, consistent with current standards.

4. Facilities and resources. Specialized pulmonary hypertension referral units should be located in tertiary care hospitals with adequate facilities and resources to these patients. The minimum requirements for such units would include the ability to carry out echocardiography and assess cardiac hemodynamics. Also necessary would be a pulmonary function laboratory, a cardiopulmonary stress testing unit, a sleep laboratory, and a radiodiagnostic department able to perform spiral CT angiography and high resolution CT. Departments specialized in nuclear medicine, respiratory medicine and cardiology should also be available.

In addition, the following services or facilities are highly desirable: a lung and/or heart-lung transplant team, a pulmonary angiography service, specialists in autoimmune diseases (internal medicine, rheumatology), an HIV clinic, cardiac and noncardiac thoracic surgeons and teams specialized in pulmonary thromboendarterectomy and liver transplantation, and/or specialists in liver hemodynamics.

5. Standard operating procedures. The referral unit should have properly updated standard operating procedures for diagnosis and treatment. The following areas should be covered: tests of hemodynamic function and vasoreactivity; TTE and transesophageal echocardiography; 6-minute walk test and incremental exercise testing; radiodiagnostics for patients with pulmonary hypertension due to chronic thrombotic and/or embolic disease; permanent intravenous catheter implantation; intravenous, subcutaneous and inhaled administration of drugs; management of right heart failure; intensive care unit admission; indication for transplantation; and procedures in terminal cases.

The operating procedures should be revised annually. The validity of the diagnostic tests should be analyzed, the level of appropriateness of previously established indications assessed, and the rates of procedural complications calculated. External auditing of compliance should be scheduled.

6. Data storage and retrieval system. Electronic databases should be used so that information on actions taken and results found and their evaluation can be retrieved. Patients should be listed in a database that incorporates their particulars, diagnosis, and results of follow-up tests.

7. Research program. The unit should undertake research that contributes to the understanding of pulmonary hypertension. Original studies should be designed and conducted and the unit should also participate in national and international trials, contribute to case registries, and publish in scientific journals.

#### 6.2. Services a Referral Unit Should Offer

1. Specialized visits. The visits for the initial evaluation of the patient's condition and follow-up should be specialized. To operate properly, the unit's office will require a) a nurse trained in the care of patients with this disease and the operation of drug delivery devices (infusion pumps, inhalation systems, permanent central venous catheters); b) a computer network giving access to the patient's records, laboratory data, and examinations performed; and c) appropriate equipment (x-ray film viewer, blood pressure monitor, electrocardiograph, pulse oximeter).

2. Diagnostic procedures. The unit must have access to the resources needed to establish a diagnosis of class and type of pulmonary hypertension, including the patient's hemodynamic status, vasoreactivity, and exercise tolerance. Centers that particularly specialize in pulmonary hypertension due to chronic thrombotic and/or embolic disease and thromboendarterectomy must be able to locate thrombotic lesions by such means as pulmonary angiography and spiral CT angiography.

3. Therapeutic procedures. The unit must have the resources to administer the various drug therapies available in their different modes of delivery. Specifically, the team must be capable of inserting a permanent central venous catheter to administer epoprostenol if necessary and be prepared to manage that treatment: there must be a nurse specialist, an informative program for the patient and family, and operating procedures for handling complications or adverse effects.

It is useful for a referral center to have teams capable of performing nonmedical treatments (interatrial septostomy, lung or heart-lung transplants, pulmonary thromboendarterectomy) in coordination with the pulmonary hypertension unit. If that capability is not present, the pulmonary hypertension unit should establish protocols stipulating the criteria governing the transfer of a patient to other specialized units and should coordinate with such units.

**TABLE 9**  
**Indications for Referral to a Specialized Pulmonary Hypertension Unit**

<p>Once left heart disease is excluded as a probable cause of elevated PASP:</p> <ol style="list-style-type: none"> <li>1. Echocardiographic evidence of moderate-severe pulmonary hypertension with PASP &gt;45 mm Hg<sup>a</sup> Symptoms suggestive of pulmonary hypertension (functional classes II-IV) Perfusion defects (possible pulmonary hypertension due to chronic thrombotic and/or embolic disease) PASP &gt;55 mm Hg if there is chronic respiratory disease (disproportionate pulmonary hypertension)</li> <li>2. Evidence of right ventricular dysfunction Signs and symptoms of heart failure Echocardiographic evidence of right ventricular enlargement and dysfunction</li> </ol>
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Abbreviation: PASP, pulmonary artery systolic pressure.  
<sup>a</sup> In the absence of systemic hypertension, obesity, or advanced age, PASP should be 55 mm Hg for referral in these circumstances.

4. Hospital facilities. A specific area of the hospital should be available to admit patients who need care that cannot be provided on an outpatient basis (because integrated care is required or in case of serious deterioration of the patient's condition). In-hospital care may also be advisable in order to perform specific diagnostic or

**TABLE 10**  
**Distribution of Functions Between the Local Hospital and the Specialized Pulmonary Hypertension Unit**

<p>Local clinic</p> <ul style="list-style-type: none"> <li>Diagnosis of suspicion of pulmonary hypertension</li> <li>Initial diagnostic work-up             <ul style="list-style-type: none"> <li>Chest radiographs, electrocardiogram, lung function tests</li> <li>Transthoracic echocardiogram</li> <li>Ventilation-perfusion lung scan (scintigraphy)</li> <li>Arterial blood gas analysis</li> </ul> </li> <li>Refer the patient to a specialized center</li> <li>Regular follow-up of the patient who has started specific treatment             <ul style="list-style-type: none"> <li>Check kidney and liver function, electrolyte balance</li> <li>Adjust dosages for conventional treatments (diuretics, oxygen, oral anticoagulants)</li> </ul> </li> <li>Arrange for emergency care at the hospital nearest the patient</li> </ul> <p>Specialized pulmonary hypertension referral unit</p> <ul style="list-style-type: none"> <li>Complete the diagnostic study             <ul style="list-style-type: none"> <li>Study of pulmonary hemodynamics and acute vasodilator test</li> <li>Pulmonary angiography if indicated</li> <li>Stress test</li> </ul> </li> <li>Select and initiate specific treatment</li> <li>Monitoring of the patient's progress             <ul style="list-style-type: none"> <li>Follow-up visits every 3-6 mo, according to clinical status</li> <li>Modification of the treatment plan, according to clinical course</li> <li>Direct assistance for the patient or support for the local care unit in case of clinical deterioration, complications of treatment, or severe intercurrent processes</li> <li>Order special procedures (transplant, thromboendarterectomy, interatrial septostomy)</li> <li>Major surgery, monitoring of pregnancy and childbirth</li> </ul> </li> </ul>
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therapeutic procedures. Admission to the day hospital may be sufficient for patients who are in stable condition.

5. Twenty-four hour care. Specialized referral units should be able to guarantee patients' access to this level of care around the clock. In particular the unit should always stand ready to solve problems that arise from the use of the various devices and systems for administering drugs.

**7. The Patient's Clinical Pathway**

The initial diagnosis of suspected pulmonary hypertension is usually made by specialists,<sup>19</sup> who may be cardiologists, pneumologists, internists, or rheumatologists working in hospitals near the patient's place of residence. Once clinical suspicion is present, the patient may have to be referred to a specialized pulmonary hypertension unit. The indications for such referral are specified in Table 9.

Once diagnosis has been made, follow-up should be coordinated between the local hospital and the specialist referral unit. Table 10 gives a brief summary of how those centers should distribute their responsibilities.

Communication between them must be fluid, facilitated by:

1. A complete referral form on the patient's history sent from the local unit to the specialized unit
2. A report from the specialized unit to the local one after each patient visit, detailing the current treatment and particular problems that require monitoring
3. The means for rapid contact between the personnel of each unit (telephone, e-mail, fax)
4. A guarantee of prompt diagnostic evaluation and start of treatment, particularly in more serious cases
5. Basic information concerning diagnostic and treatment protocols for use in pulmonary hypertension, provided by the specialist referral unit for the benefit of the local hospital. The 2 centers should come to an agreement on the best way to comply with the requirements of those protocols.

**7.1. Timing**

– Given the seriousness of a diagnosis of pulmonary hypertension, there should be no delay between clinical suspicion and carrying out TTE, particularly when either PAH or pulmonary hypertension due to chronic thrombotic and/or embolic disease is suspected or when symptoms are severe (functional classes III or IV). In such circumstances TTE scheduling should give preference to these patients and not be delayed beyond 4 weeks.

– When a patient is referred to a pulmonary hypertension unit, no more than 3 to 4 weeks should pass before the first specialized visit takes place, and no more than another 3 to 4 weeks before the first hemodynamic evaluation is performed.

– Once the type of pulmonary hypertension has been diagnosed and hemodynamics assessed, treatment should be started within 15 days.

– Follow-up visits with stable patients whose progress is satisfactory (functional classes I or II) may be scheduled every 3 weeks at the local clinic and every 6 months at the specialized referral unit.

– If there is significant clinical deterioration or serious treatment-related complications, the patient should be attended at the referral center within 24 hours.

Patients generally continue to require care at the specialized unit until death or until a transplant is carried out. Palliative care of patients with irreversible pulmonary hypertension in advanced stages should be arranged between the local center and the referral unit and should be carried out in a coordinated way.

### 7.2. Special Situations

In certain situations, some patients with pulmonary hypertension may need to undergo procedures requiring a maximum level of expertise. Such cases are special and it is not necessary for those procedures to be included in the list of characteristics of specialized referral units. It is for that reason that units should coordinate with others and establish protocols for referring patients to more specialized centers. Such circumstances develop in the contexts of congenital heart disease, lung or heart-lung transplants, and pulmonary thromboendarterectomy.

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