2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

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ESC/ERS GUIDELINES

Changes from the 2009 ESC/ERS guidelines

- La RVP se ha incluido en la definición hemodinámica de la HAP
- La clasificación clínica para pacientes adultos y pediátricos se ha actualizado
- Se actualiza el algoritmo diagnóstico.
- Se reportan nuevos avances en materia de evaluación de gravedad HAP y sobre los tratamientos y los objetivos del tratamiento.
- En consecuencia el algoritmo de tratamiento se ha actualizado

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Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

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3. DEFINITIONS AND CLASSIFICATIONS

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Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥ 25 mmHg	All
Pre-capillary PH	PAPm ≥ 25 mmHg PAWP ≤ 15 mmHg	1. Pulmonary arterial hypertension (PAH) 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post capillary PH	PAPm ≥ 25 mmHg PAWP > 15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG < 7 mmHg and/or PVR ≤ 3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥ 7 mmHg and/or PVR > 3 WU[c]	

[a]All values measured at rest. [b]According to the clinical classification of PH. [c]Wood Units are preferred to dynes.s.cm^{-5}.

DPG: diastolic pressure gradient (diastolic PAP – mean PAWP).
PAH: Pre-capillary PH + PVR > 3 WU

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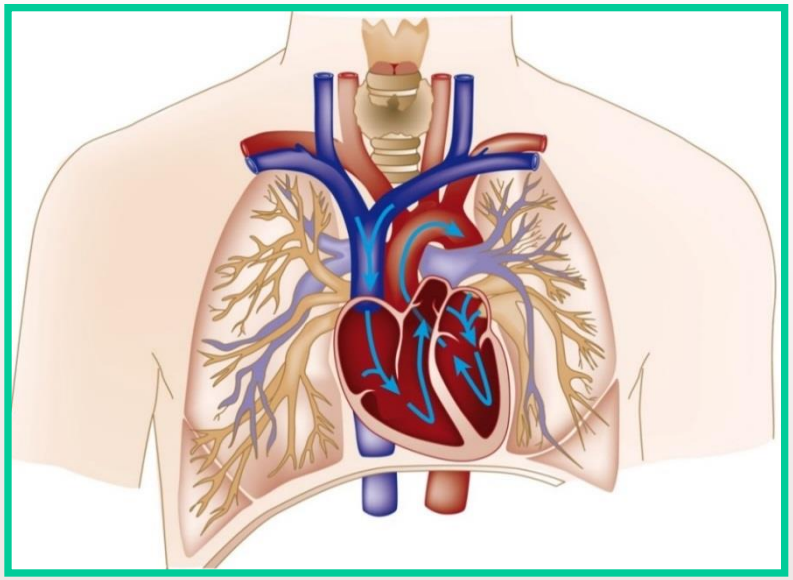
Clinical classification overview

1. PAH

- 1.1 Idiopathic PAH (iPAH)
- 1.2 Heritable PAH
- 1.3 Drug and toxin induced
- 1.4 Associated with (APAH):
  - 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 haemangiomatosis

1''. Persistent PH of the newborn (PPHN)

2. PH due to left heart disease

3. PH due to lung disease and/or hypoxia

4. Chronic thromboembolic PH and other pulmonary artery obstructions

5. PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders
- 5.2 Systemic disorders
- 5.3 Metabolic disorders
- 5.4 Other

Niños incluidos en diferentes grupos
Otras mutaciones para PAH y PVO
Anemia hemolitica cronica pasa del 1 al 5
Patologia pediátrica izquierda en grupo 2
Desarrollo de los grupos de Veno-oclusiva y HPTEC

Clinical classification

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (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 haemangiomatosis
1'.1 Idiopathic
1'.2 Heritable
1'.2.1 EIF2AK4 mutation
1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
1'.4.1 Connective tissue disease
1'.4.2 HIV infection
1". Persistent pulmonary hypertension of the newborn

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Clinical classification continued

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 left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital /acquired pulmonary vein stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

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Clinical classification continued

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 tumours
4.2.3 Arteritis
4.2.4 Congenital pulmonary artery stenosis
4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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Important pathophysiological and clinical definitions

1. Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure ≥25 mmHg at rest as assessed by right heart catheterization (Table 3). PH can be found in multiple clinical conditions (Table 4).

2. Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of pre-capillary PH (Table 3) and pulmonary vascular resistance >3 Wood units, in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases (Table 4). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation (Table 4).

3. There is no sufficient data to support the definition of 'PH on exercise'.

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4. EPIDEMIOLOGY AND GENETICS OF PULMONARY HYPERTENSION

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EPIDEMIOLOGY AND GENETICS OF PULMONARY HYPERTENSION

- En Europa la prevalencia de la HAP es 15-60 casos/millón y la incidencia 5-10/millón/año.
- Grupo 2 hasta 60% con ICC grave y 70% en IC con FE preservada. Altisima en patología mitral grave y hasta el 65% en Eao sintomática
- Los avances en genética se han centrado en los pacientes con HAPI, HAPH (*BMPR2* , *BMPR1B, CAV1, KCNK3*) y EVOP (*EIF2AK4*).
- No se ha encontrado ningún sustrato formas asociadas de HAP o en HP de los grupos 2 al 5.

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5. PULMONARY HYPERTENSION DIAGNOSIS

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PULMONARY HYPERTENSION DIAGNOSIS

- La introducción del concepto de "equipo multidisciplinario", que incluya al menos un cardiólogo, un neumólogo y un experto en imagen.
- En las PFR destaca el papel del *DLCO*.
  - Si es menor del 45%, obliga a estudiar detenidamente patología respiratoria asociada y a descartar EVOP.
  - La DLCO baja es un marcador de mal pronóstico.

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ECOCARDIOGRAMA

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

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sintomáticos

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[d]	Class[a]	Level[b]	With risk factors or associated conditions for PAH or CTEPH[c]	Class[a]	Level[b]	Ref[c]
Low	Alternative diagnosis should be considered	IIa	C	Echo follow-up should be considered	IIa	C	
Intermediate	Alternative diagnosis, echo follow-up, should be considered	IIa	C	Further assessment of PH including RHC should be considered[e]	IIa	B	45, 46
	Further investigation of PH may be considered[e]	IIb					
High	Further investigation of PH (including RHC[e]) is recommended	I	C	Further investigation of PH[e] including RHC is recommended	I	C	

asintomáticos

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[d,e]	Class[a]	Level[b]	With risk factors or associated conditions for PAH or CTEPH[d,e]	Class[a]	Level[b]	Ref[c]
Low	No work up for PAH required	III	C	Echo follow-up may be considered	IIb	C	
Intermediate	Echo follow-up should be considered	IIa	C	Echo follow-up is recommended	I	B	67, 76, 88
				If associated scleroderma, RHC should be considered[f]	IIa	B	8, 17, 29
High	RHC should be considered[f]	IIa	C	RHC is recommended	I	C	

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Recommendations	Class[a]	Level[b]	Ref.[c]
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (group 1) and to support treatment decisions	I	C	
In patients with PH, it is recommended to perform RHC in expert centres (see section 12) as it is technically demanding and may be associated with serious complications	I	B	69
RHC should be considered in pulmonary arterial hypertension (group 1) to assess the treatment effect of drugs (Table 16)	IIa	C	
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 24)	I	C	
RHC is recommended in patients with PH due to left heart disease (group 2) or lung disease (group 3) if organ transplantation is considered	I	C	
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP	IIa	C	
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions	IIb	C	
RHC is indicated in patients with CTEPH (group 4) to confirm the diagnosis and support treatment decisions	I	C	

Recommendations	Class[a]	Level[b]	Ref.[c]
Vasoreactivity testing is indicated only in expert centres	I	C	69
Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB	I	C	84,85
A positive response to vasoreactivity testing is defined as a reduction of mean PAP $\geq$10 mmHg to reach an absolute value of mean PAP $\leq$40 mmHg with an increased or unchanged cardiac output	I	C	85,86
Nitric oxide is recommended for performing vasoreactivity testing	I	C	85,86
Intravenous epoprostenol is recommended for performing vasoreactivity testing as an alternative	I	C	85,86
Adenosine should be considered for performing vasoreactivity testing as an alternative	IIa	C	87,88
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative	IIb	C	89,90
The use of oral or intravenous CCBs in acute vasoreactivity testing is not recommended	III	C	
Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use and is not recommended in PH groups 2, 3, 4 and 5	III	C	

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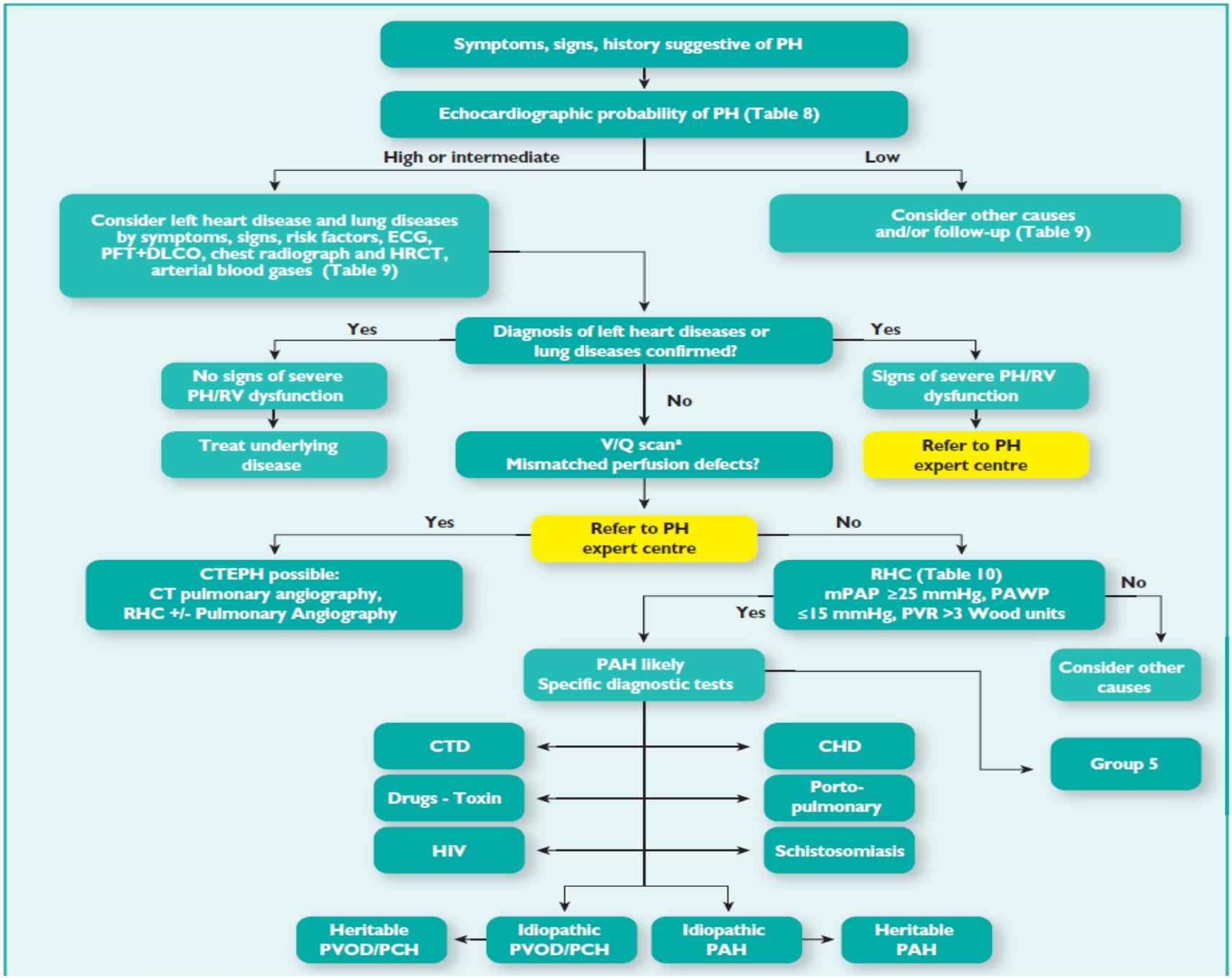
ESTUDIO HEMODINAMICO

TEST DE VASORECTIVIDAD


Symptoms, signs, history suggestive of PH
Echocardiographic probability of PH (Table 8)
High or intermediate
Low
Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases (Table 9)
Consider other causes and/or follow-up (Table 9)
Diagnosis of left heart diseases or lung diseases confirmed?
Yes
Yes
No
No signs of severe PH/RV dysfunction
Signs of severe PH/RV dysfunction
Treat underlying disease
V/Q scan[a] Mismatched perfusion defects?
Refer to PH expert centre
Yes
No
Refer to PH expert centre
CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography
RHC (Table 10) mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
Yes
No
PAH likely Specific diagnostic tests
Consider other causes
CTD
CHD
Group 5
Drugs - Toxin
Porto-pulmonary
HIV
Schistosomiasis
Heritable PVOD/PCH
Idiopathic PVOD/PCH
Idiopathic PAH
Heritable PAH

ESTRATEGIA DIAGNOSTICA

Recommendations	Class[a]	Level[b]	Ref.[c]
Echocardiography is recommended as a first-line non-invasive diagnostic investigation in case of suspicion of PH	I	C	
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to exclude CTEPH	I	C	47
Contrast CT angiography of the PA is recommended in the workup of patients with CTEPH	I	C	93
Routine biochemistry, haematology, immunology, HIV testing and thyroid function tests are recommended in all patients with PAH to identify the specific associated condition	I	C	
Abdominal ultrasound is recommended for the screening of portal hypertension	I	C	67
Lung function test with DLCO is recommended in the initial evaluation of patients with PH	I	C	36
High-resolution CT should be considered in all patients with PH	IIa	C	94
Pulmonary angiography should be considered in the workup of patients with CTEPH	IIa	C	
Open or thoracoscopic lung biopsy is not recommended in patients with PAH	III	C	

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6. PULMONARY ARTERIAL HYPERTENSION (GROUP 1)

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Risk assessment in PAH

Determinants of prognosis[a]	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	> 440 m	165-440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 ml/min/kg (> 65% pred.) VE/VCO_2 slope < 36	Peak VO_2 11-15 ml/min/kg (35-65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 < 11 ml/min/kg (< 35% pred.) VE/VCO_2 ≥ 45
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/ml	BNP 50-300 ng/l NT-proBNP 300-1400 ng/l	BNP > 300 ng/l NT-proBNP > 1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area < 18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal, pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Haemodynamics	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%

[a]Estimated 1-year mortality. [b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient. [c]Repeated episodes of syncope, even with little or regular physical activity.

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SEGUIMIENTO

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

[b]Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP.
[c]Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient needs.
[d]From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.

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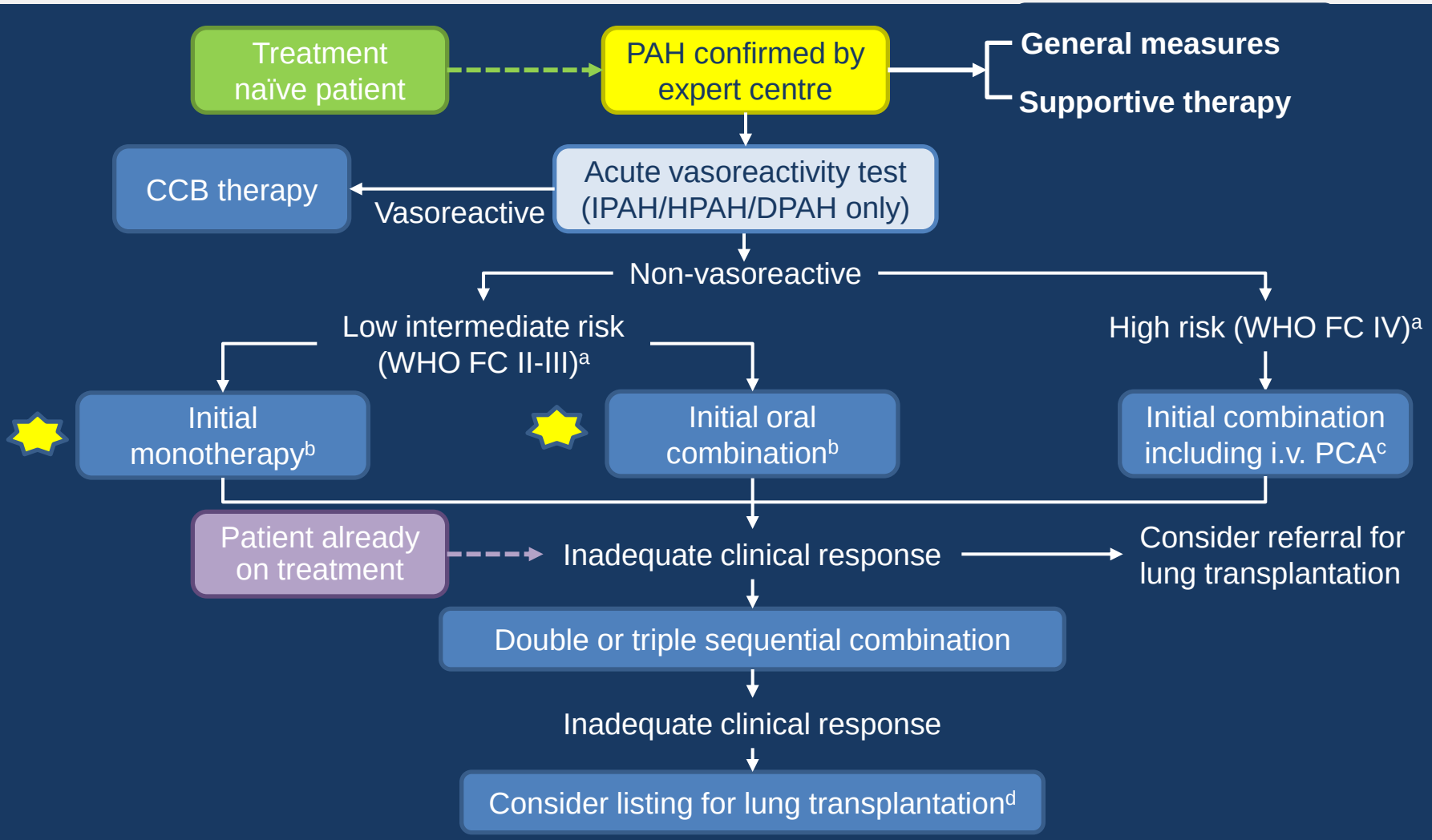
EVALUACION DE GRAVEDAD Y SEGUMIENTO

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations (*Tables 13* and *14*)	I	C	96,97, 99
It is recommended to perform regular follow-up assessments every 3–6 months in stable patients (*Table 14*)	I	C	98
Achievement/maintenance of a low-risk profile (*Table 13*) is recommended as an adequate treatment response for patients with PAH	I	C	96–99
Achievement/maintenance of an intermediate-risk profile (*Table 13*) should be considered an inadequate treatment response for most patients with PAH	IIa	C	96–99

Evidence based treatment algorithm



[a]Some WHO-FC III patients may be considered high risk; [b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure; [c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy; [d]Consider also balloon septostomy.

Medidas generales y terapia de soporte

Recommendations	Class[a]	Level[b]
It is recommended that PAH patients avoid pregnancy	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C
Psychosocial support is recommended in PAH patients	I	C
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	IIa	C
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	III	C

Recommendations	Class[a]	Level[b]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[d]	I	C
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C

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Tratamiento inicial en monoterapia

			Class[a]-Level[b]					
			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C[d]	I	C[d]	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[e]		I	B	I	B	IIb	C
Phosphodiesterase type 5 inhibitors ev	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil[g]		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous[g]	-	-	IIa	C	IIb	C
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C
		Inhaled[g]	-	-	I	B	IIb	C
		Intravenous[f]	-	-	IIa	C	IIb	C
		Oral[g]	-	-	IIb	B	-	-
	Beraprost[g]		-	-	IIb	B	-	-
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-

En los ensayos clínicos actuales el objetivo primario es el tiempo hasta el deterioro o el evento clínico, o la mortalidad por cualquier causa

Tratamiento inicial en combinacion

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC I		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C

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Tratamiento secuencial en combinacion

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	–	–	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	–	–	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

Controlled trials

Macitentan	SERAPHIN[16]	742	115	No, or Sildenafil, or Inh iloprost	TTCW	TTCW improved in monotherapy and combination
Riociguat	PATENT[17]	443	12	No, or bosentan, or prostanoids	6MWD	6MWD improved Haemodynamics improved
	PATENT plus[18]	30	18	Sildenafil	Supine SBP	Terminated for excess of SAE in the treated group
Selexipag[a]	Phase - 2[39]	43	17	ERA and/or PDE-5i	PVR	PVR improved 6MWD not improved
	GRIPHON[40]	1156	74	ERA and/or PDE-5i	TTCW	TTCW improved
Ambrisentan or tadalafil vs ambrisentan + tadalafil	AMBITION[42]	500	78	No	TTCF	TTCF improved 6MWD improved

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Tratamiento del paciente critico

Right ventricle assistance
The use of veno-arterial extracorporeal membrane oxygenation (ECMO) should be considered for selected patients with PH and RV failure.

FE/Flutter occurred with an incidence of 2.8%. Persistent atrial fibrillation was associated with a 2-year mortality 80%. Electric cardioversion and radiofrequency ablation in refractory cases have proven to be effective

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Hospitalization in ICU is recommended in PH patients with high heart rate (>110 beats/ min), low blood pressure (systolic blood pressure <90 mmHg), low urine output and rising lactate levels due or not due to co-morbidities	–	–	–	–	I	C
Inotropic support is recommended in hypotensive patients			I	C	I	C
Lung transplantation is recommended soon after inadequate clinical response on maximal medical therapy	–	–	I	C	I	C
BAS may be considered where available after failure of maximal medical therapy	–	–	IIb	C	IIb	C

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7. SPECIFIC PULMONARY (ARTERIAL) HYPERTENSION SUBSETS

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Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger's syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

2. PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable[a]
- Non-correctable

Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental defects[b]

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

1. Type

- **1.1 Simple pre-tricuspid shunts**
  - 1.1.1 Atrial septal defect (ASD)
    - 1.1.1.1 Ostium secundum
    - 1.1.1.2 Sinus venosus
    - 1.1.1.3 Ostium primum
  - 1.1.2 Total or partial unobstructed anomalous pulmonary venous return
- **1.2 Simple post-tricuspid shunts**
  - 1.2.1 Ventricular septal defect (VSD)
  - 1.2.2 Patent ductus arteriosus
- **1.3 Combined shunts**
  - Describe combination and define predominant defect
- **1.4 Complex congenital heart disease**
  - 1.4.1 Complete atrioventricular septal defect
  - 1.4.2 Truncus arteriosus
  - 1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
  - 1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
  - 1.4.5 Other

2. Dimension (specify for each defect if more than one congenital heart defect exists)

- **2.1 Haemodynamic (specify Qp/Qs)[a]**
  - 2.1.1 Restrictive (pressure gradient across the defect)
  - 2.1.2 Non-restrictive
- **2.2 Anatomic[b]**
  - 2.2.1 Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
  - 2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)

3. Direction of shunt

- 3.1 Predominantly systemic-to-pulmonary
- 3.2 Predominantly pulmonary-to-systemic
- 3.3 Bidirectional

4. Associated cardiac and extracardiac abnormalities

5. Repair status

- 5.1 Unoperated
- 5.2 Palliated (specify type of operation/s, age at surgery)
- 5.3 Repaired (specify type of operation/s, age at surgery)

Recomendaciones para HAP en pacientes con CC del adulto y su corrección.

Recommendations			Class[a]	Level[b]
PVRi (WU • m^2)	PVR (WU)	Correctable[d]		
<4	<2.3	Yes	IIa	C
>8	>4.6	No	IIa	C
4–8	2.3–4.6	Individual patient evaluation in tertiary centres	IIa	C

Correccion quirúrgica o pecutanea

Recommendations	Class[a]	Level[b]
Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome	I	B
Other ERAs, PDE-5is and prostanoids should be considered in patients with Eisenmenger syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with PA thrombosis or signs of heart failure	IIb	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial O_2 saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%	IIa	C
The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels	IIb	C
Combination drug therapy may be considered in patients with Eisenmenger syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger syndrome	III	C

Pulmonary arterial hypertension associated with connective tissue disease

Recommendations	Class[a]	Level[b]
In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended	I	C
Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO and biomarkers	I	C
RHC is recommended in all cases of suspected PAH associated with CTD	I	C
Oral anticoagulation may be considered on an individual basis and in the presence of thrombophilic predisposition	IIb	C

Recomendaciones para screening de HP

Recommendations	Class [a]	Level [b]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C

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Recomendaciones para HAP asociada a hipertensión portal y a VIH

Recommendations	Class[a]	Level[b]
Echocardiographic screening in asymptomatic HIV patients to detect PH is not recommended	III	C
In patients with PAH associated with HIV infection, the same treatment algorithm used for patients with PAH should be considered, taking into consideration co-morbidities and drug–drug interactions	IIa	C
Anticoagulation is not recommended because of a lack of data on the efficacy:risk ratio	III	C

Recommendations	Class[a]	Level[b]
Echocardiographic assessment for signs of PH is recommended in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation	I	B
It is recommended that patients affected by PAH associated with portal hypertension should be referred to centres with expertise in managing both conditions	I	C
It is recommended that the treatment algorithm for patients with other forms of PAH should be applied to patients with PAH associated with portal hypertension, taking into account the severity of liver disease	I	C
Anticoagulation is not recommended in patients with PH associated with portal hypertension	III	C
Liver transplantation may be considered in selected patients responding well to PAH therapy	IIb	C
Liver transplantation is contraindicated in patients with severe and uncontrolled PAH	III	C

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Recomendaciones para la enfermedad venooclusiva pulmonar y la hemangionmatosis capilar

Recommendations	Class[a]	Level[b]
A combination of clinical findings, physical examination, bronchoscopy and radiological findings is recommended to diagnose PVOD/PCH	I	C
Identification of a bi-allelic *EIF2AK4* mutation is recommended to confirm a diagnosis of heritable PVOD/PCH without histological confirmation	I	B
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is indicated as soon as the diagnosis is established	I	C
Patients with PVOD/PCH should be managed only in centres with extensive experience in PH due to the risk of lung oedema after the initiation of PAH therapy	IIa	C

8. PULMONARY HYPERTENSION DUE TO LEFT HEART DISEASE (GROUP 2)

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Recomendaciones para la HP por cardiopatia izquierda

Definition	Characteristics[a]	Clinical group(s)[b]
Post capillary PH	PAPm ≥ 25 mmHg PAWP > 15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG < 7 mmHg and/or PVR ≤ 3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥ 7 mmHg and/or PVR > 3 WU[c]	

Recomendaciones para la HP por cardiopatia izquierda

Clinical presentation	Echocardiography	Other features
Age >65 years	Structural left heart abnormality • Disease of left heart valves • LA enlargement (>4.2 cm) • Bowing of the IAS to the right • LV dysfunction • Concentric LV hypertrophy and/or increased LV mass	ECG • LVH and/or LAH • AF/Afib • LBBB • Presence of Q waves
Symptoms of left heart failure	Doppler indices of increased filling pressures • Increased E/e' • >Type 2–3 mitral flow abnormality	Other imaging • Kerley B lines • Pleural effusion • Pulmonary oedema • LA enlargement
Features of metabolic syndrome	Absence of • RV dysfunction • Mid systolic notching of the PA flow • Pericardial effusion	
History of heart disease (past or current)		
Persistent atrial fibrillation		

Recommendations	Class[a]	Level[b]
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease)	I	B
It is recommended to identify other causes of PH (i.e. COPD, sleep apnoea syndrome, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD	I	C
It is recommended to perform invasive assessment of PH in patients on optimized volume status	I	C
Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic workup and an individual treatment decision	IIa	C
The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation	III	C
The use of PAH-approved therapies is not recommended in PH-LHD	III	C

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9. PULMONARY HYPERTENSION DUE TO LUNG DISEASES AND/OR HYPOXIA (GROUP 3)

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Recomendaciones para la HP por enfermedad pulmonar

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

Recommendations	Class[a]	Level[b]
Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease	I	C
Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction	I	C
The optimal treatment of the underlying lung disease, including long-term O_2 therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases	I	C
Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment	IIa	C
RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial)	III	C
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C

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10. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (GROUP 4)

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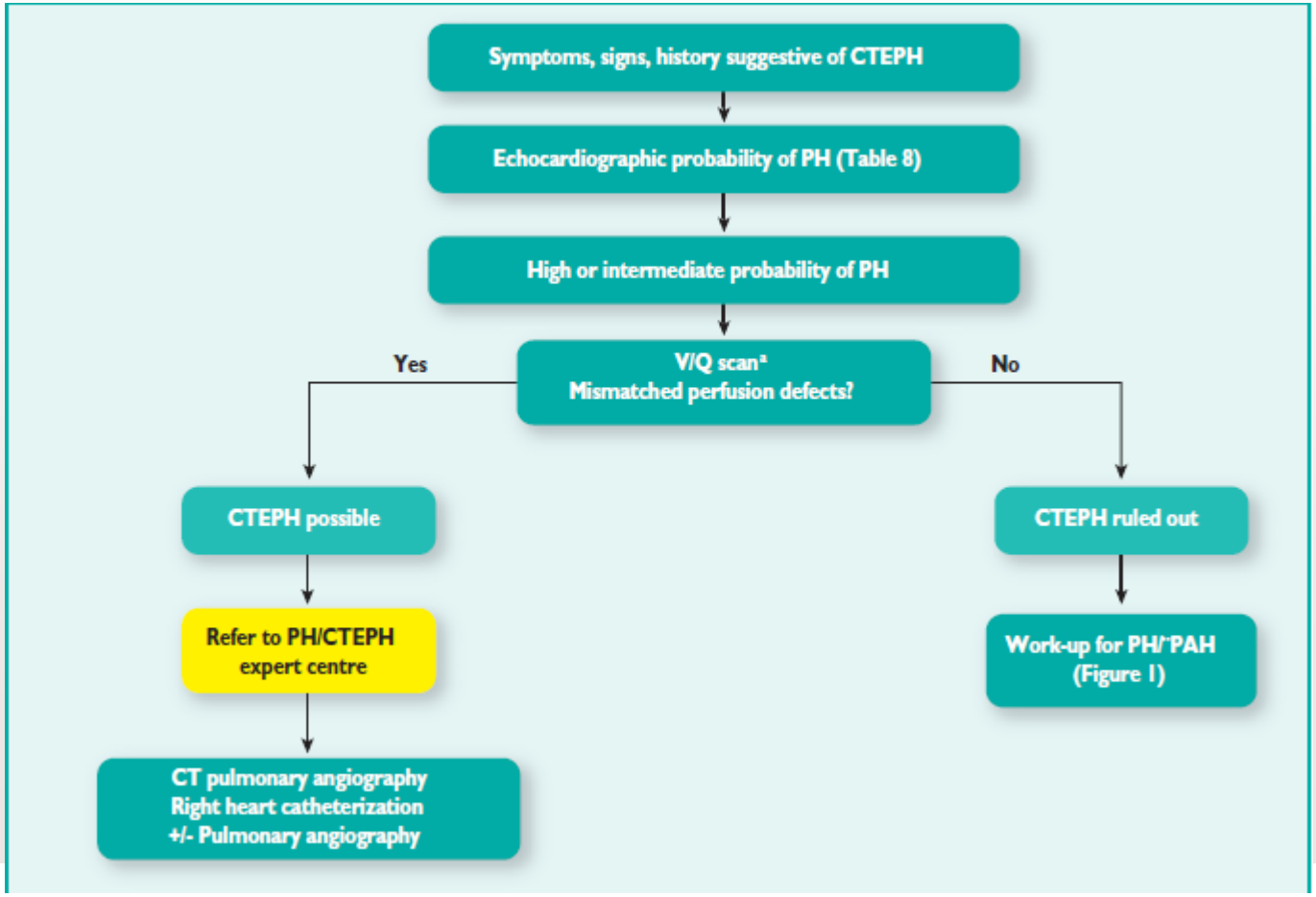
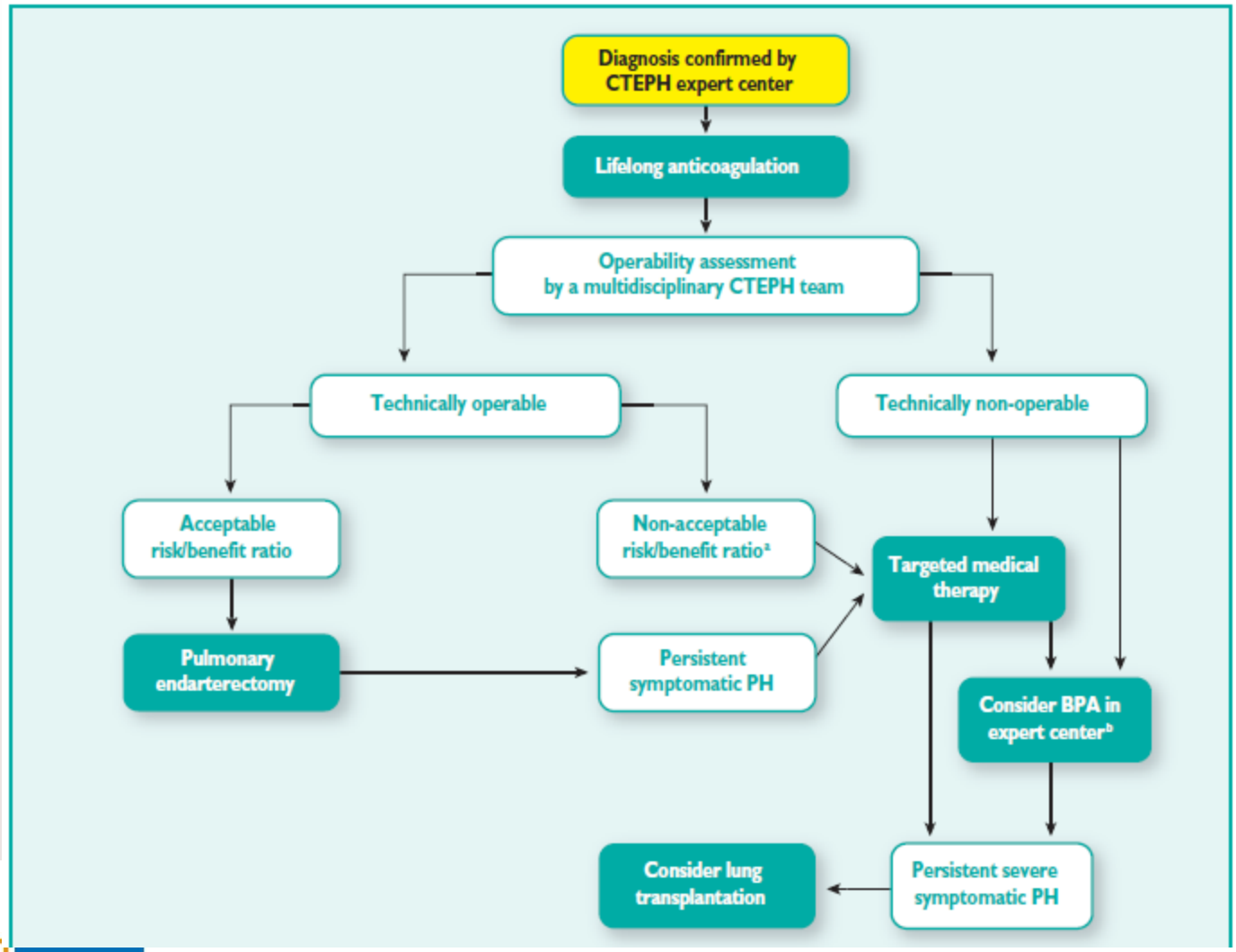
Recomendaciones para la hipertensión pulmonar tromboembólica crónica HPTC



Recomendaciones para la hipertensión pulmonar tromboembólica crónica HPTC



Recomendaciones para la hipertensión pulmonar tromboembólica crónica HPTC

Recommendations	Class[a]	Level[b]
In PE survivors with exercise dyspnoea, CTEPH should be considered	IIa	C
Life-long anticoagulation is recommended in all patients with CTEPH	I	C
It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies should be made by a multidisciplinary team of experts	I	C
Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH	I	C
Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	IIb	B
Interventional BPA may be considered in patients who are technically non-operable or carry an unfavourable risk:benefit ratio for PEA	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended	III	C

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12. DEFINITION OF A PULMONARY HYPERTENSION REFERRAL CENTRE

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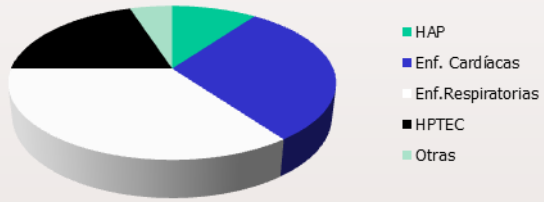
Recomendaciones para centros de referencia en hipertensión pulmonar

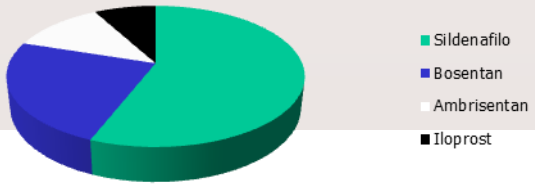
Unitat de HP del Mar

Centre associat a la U.E.H.P. de l'Hospital Clínic

Pacientes con CCD (118)



Tratamientos específicos
24 pacientes



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Recommendations	Class[a]	Level[b]
It is recommended for referral centres to provide care by a multiprofessional team (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise)	I	C
It is recommended for referral centres to have direct links and quick referral patterns to other services (such as CTD, family planning, PEA, lung transplantation, adult congenital heart disease)	I	C
It should be considered that a referral centre follow at least 50 patients with PAH or CTEPH and should receive at least two new referrals per month with documented PAH or CTEPH	IIa	C
It should be considered that a referral centre perform at least 20 vasoreactivity tests in IPAH, HPAH or DPAH patients per year	IIa	C
Referral centres should participate in collaborative clinical research in PAH, including phase II and phase III clinical trials	IIa	C

Aspectos relevantes y novedosos

Definición y epidemiología
En la definición hemodinámica de HAP se completa la PAPm>25 mm Hg con un valor de RVP >3 UW
Se introduce una nueva definición hemodinámica para la HP combinada precapilar y poscapilar: gradiente diastólico ≥ 7 mm Hg y RVP >3 UW
Se incorporan los nuevos avances genéticos en HAPI, HAPH y en HP venoclusiva. Se recomienda el estudio genético y el consejo genético al diagnóstico de la enfermedad

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Aspectos relevantes y novedosos

Diagnóstico
El *screening* anual en los pacientes con esclerodermia (ecocardiograma, DLCO y ProBNP) asintomáticos (IC)
La DLCO debe realizarse siempre al diagnóstico (IC)
En el ecocardiograma se distinguen tres niveles de probabilidad de presentar hipertensión pulmonar, bajo, medio y alto. En base a la velocidad máxima de regurgitación tricúspide y a la presencia de "signos ecocardiográficos de hipertensión pulmonar"
La valoración global del ecocardiograma y del riesgo de desarrollar HP determinarán la indicación de realizar CCD
El CCD es imprescindible para diagnosticar de HPTEC (IC)
Se especifica la sistemática para realizar el CCD y el test vasodilatador y se recomienda su realización en centro experto (IC)

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Aspectos relevantes y novedosos

Pronóstico
Se realiza una clasificación según el riesgo de los pacientes en *tres* grupos, asignando una probabilidad de mortalidad a 1 año: riesgo bajo (<5%), intermedio (5-10%) y alto (>10%)
Se recomienda la valoración multifactorial de elementos clínicos, bioquímicos, capacidad funcional, ecocardiográficos y hemodinámicos de forma regular (IC)
Los pacientes se consideran bien controlados cuando tienen un perfil de riesgo bajo (IC)

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Aspectos relevantes y novedosos

Tratamiento
Recomendación en CF II y III de iniciar tratamiento combinado de entrada o monoterapia
El trasplante pulmonar se debe indicar precozmente ante el fallo del tratamiento (IC). El paciente con HP venooclusiva debe referirse para trasplante pulmonar al diagnóstico
Se establecen unos límites hemodinámicos para reparar los *shunts* sistémico-pulmonares en los pacientes con CC y HAP
En los pacientes con HP del grupo 2 y del grupo 3 el tratamiento con fármacos específicos para la HAP no está indicado (IIIC)
Todo paciente con HPTEC deber ser valorado en un centro experto (con cirujano especializado en endarterectomía pulmonar).
El riociguat está indicado en la HPTEC no Q o con HP persistente tras la Q (IB)

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Aspectos controvertidos o sin concretar

Definición y diagnóstico
No se define la HP con el ejercicio
No se estandariza la realización del test de sobrecarga de volumen o el cateterismo de ejercicio para discriminar la HP del grupo 2 y la HAP
No se estandariza la realización del test de esfuerzo cardiopulmonar con consumo de oxígeno
No hay suficiente evidencia científica que sustente los puntos de corte seleccionados en las distintas pruebas que estratifican el pronóstico
Tratamiento
Falta de estandarización de los programas de rehabilitación.
Ausencia de acuerdo en la selección de la planificación familiar.
No se especifica si en los pacientes en CF II-III es mejor el tratamiento combinado de inicio o la monoterapia.
No se delimita en que circunstancias estaría indicado realizar tratamiento médico previo a la cirugía en los pacientes HPTEC

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MOLTES GRACIES

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