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Pulmonary hypertension: the state of the art

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ABSTRACT

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure of 25 mmHg or more at rest assessed by right heart catheterisation. It is a progressive disease characterized by high mortality and morbidity. Current PH guidelines suggest that patients with PH should be cared for in dedicated specialist centres, with expertise and resources available to provide high quality care to this fragile population. In this review, we focus on the clinical manifestations, diagnostic algorithm, risk assessment and therapeutic strategies for PH. We also provide an overview of the organisation of PH services in United Kingdom, including designation of expert centres, national audit and steps to ensure the quality and financial viability of PH care.

Introduction

Pulmonary hypertension (PH) is a progressive and debilitating condition, defined as an increase in mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, measured by right heart catheterization (RHC). It is associated with a range of underlying aetiologies, most commonly chronic left-sided cardiac disease or lung disease. In recent years, chronic thromboembolic disease (CTEPH) is increasingly recognised as a common cause of PH. This, and other rare forms of PH, including idiopathic pulmonary arterial hypertension (PAH) and PAH related to connective tissue disease (CTD) and congenital heart disease (CHD) have received significant attention, with numerous randomised trials establishing the role of PAH therapies and changing the landscape of PH.

PH is characterized by breathlessness, fatigue and psychological distress. The diagnosis of PH is often overlooked, as the typical signs and symptoms of PH are non-specific, and are similar to other more common conditions, such as asthma, chronic obstructive pulmonary disease (COPD) and heart failure. Delays in the diagnosis and management of PH can be detrimental and should be avoided through education and increased awareness of the condition, combined with early referral to expert centres.[1]

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The classification of pulmonary hypertension

Hemodynamic definition

From a hemodynamic point of view, PH can be classified on the basis of the pulmonary artery wedge pressure (PAWP) into pre-capillary (PAWP≤15 mmHg) or post-capillary (PAWP >15 mmHg, Table 1). In the latest classification, post-capillary PH is distinguished into *isolated* or *combined pre and post-capillary*, based on pulmonary vascular resistance (cut-off of 3WU) and the diastolic pressure gradient (cut-off of 7 mmHg). RHC, thus, remains essential for the diagnostic workup of PH patients and for deciding management.[1]

Examples of post-capillary PH include patients with severe systolic or diastolic left ventricle (LV) dysfunction or valve disease (*e.g.* mitral stenosis). When post-capillary PH is long-standing, or other causes of PH are present, a precapillary component can develop, resulting in combined pre- and post-capillary PH.

Cardiac catheterisation is essential for establishing

the diagnosis of PH, but requires significant expertise, which is occasionally lost in busy interventional cardiology laboratories that focus on ischemic heart disease. Small errors in measuring PAWP can lead to an erroneous classification of patients. This may be related to significant respiratory *swing*, suboptimal wedging (over or under-wedging), calibration and damping. Error can also be introduced when estimating cardiac output, ideally using either the direct Fick formula (with measurement of oxygen consumption in the cardiac catheter laboratory), thermodilution, or cardiac magnetic resonance (in hybrid laboratories).[2] Operators should be well aware of the limitations and potential pitfalls of each technique (*e.g.* thermodilution is not recommended in patients with intracardiac shunts). Finally, few laboratories are able to provide vasoreactivity testing, which is typically performed using inhaled nitric oxide or other pulmonary vasodilators. RHC is also important in assessing the severity of hemodynamic impairment, for risk stratification, to assess the effect of treatment and the progression of disease. Repeat cardiac catheterisation is, therefore, the rule for most PH patients, especially those who are deemed candidates for specific therapies.[1]

Some aspects of the PH definition and classification are still debated by experts. It is recognised that patients with *borderline* mean PA pressure between 21-24 mmHg should be monitored carefully, as studies have suggested that a mPAP >20 mmHg exceeds the upper limit of normal (normal mPAP 14±3.3 mmHg) and patients with borderline PH have a worse prognosis compared to patients with mPAP ≤20 mmHg.[1,3]

Clinical classification

The current international PH classification divides PH into 5 groups, encompassing multiple clinical conditions, which share similarities in presentation, pathological findings, haemodynamic characteristics and treatment strategy. This categorization is now accepted worldwide and used in clinical practice (Table 2).[1]

Group 1

PAH, is a disease characterized by progressive remodelling of the distal pulmonary arteries, resulting in the loss of vascular cross-sectional area and elevated pulmonary vascular resistance (PVR). PAH has different aetiologies, leading to pre-capillary pulmonary hypertension. It is termed idiopathic when no causative factors are identified and heritable when it has a possible genetic transmission.[4,5] PAH can be also induced by drugs or toxins, or can be associated with conditions, such as CTD, CHD, portal hypertension and HIV infection.

Every year, new genes associated with PAH are discovered, reiterating the importance of genetic screening in tertiary centres. Moreover, new drugs and toxins responsible for the development of PAH have been discovered in recent years: *e.g.* dasanatib is a chemotherapy drug that can induce remodelling and capillary proliferation in the pulmonary circulation, but these changes may be reversed when it is stopped. Anorexigens, such as aminorex, fenfluramine and benfluorex are the first class of medications recognized to cause PAH. Although, most of these medications have now been withdrawn worldwide, they remain important, not only from a historical perspective, but because they emphasise the role of serotonin metabolism in the pathogenesis of PAH.[5]

Group 1 also includes pulmonary veno-occlusive disease (PVOD, Group 1') and the persistent pulmonary hypertension of the newborn (Group 1''). PVOD is rare and can resemble idiopathic PAH in terms of clinical presentation and haemodynamics (raised mPAP with a normal PAWP); however, its management differs significantly, requiring early referral to lung transplantation.[1]

Group 2

Group 2 is characterized by PH secondary to left heart disease. The most frequent reason is diastolic dysfunction of the left ventricle, typically present in older patients with risk factors, such as diabetes mellitus, hypertension, hyperlipidaemia and ischemic heart disease.[6] Group 2 PH is typically postcapillary,

Table 1. Hemodynamic classification of pre and post capillary pulmonary hypertension.

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

mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; DPG, diastolic pressure gradient (diastolic pulmonary artery pressure - mean PAWP); PVR, pulmonary vascular resistance; PH, pulmonary hypertension.

but a *reactive* precapillary component may develop (combined pre and post-capillary PH, Table 1). In patients with multiple comorbidities, pre and post-capillary PH may coexist (*e.g.* in a patient with chronic thromboembolic disease or scleroderma and left ventricular diastolic dysfunction), complicating management.[1]

There is still debate on the optimal state of hydration at which patients should be hemodynamically assessed. Patients with left heart disease who have been fasting for several hours before cardiac catheterisation, may have a resting PAWP ≤15 mmHg and could be misdiagnosed as precapillary PH. In such cases, and when there is clear suspicion of a postcapillary component to the PH, some centres suggest fluid or exercise challenge during the catheter assessment. However, there is still insufficient evidence to guide the interpretation of such challenges and hence, to date, there are no clear recommendations in the PH guidelines.

Group 3

Group 3 includes patients with lung disease and PH: COPD and interstitial lung disease, mixed restrictive/obstructive, alveolar hypoxia and developmental disorders, such as congenital or bronchopulmonary dysplasia. Because exertional dyspnea is the most common symptom associated with both PH and lung disease, the presence of coexisting PH is easily overlooked.[7] The pathogenesis of PH in this group is multifactorial and may result from chronic hypoxic pulmonary vasoconstriction and vascular remodelling. Other possible mechanisms include vascular obstruction or destruction associated with progressive parenchymal fibrosis, vascular inflammation, perivascular fibrosis and thrombotic angiopathy. To date, there is no convincing evidence from randomised trials on the use of PAH therapies for patients who belong to Group 3.[8] These patients have a very poor outcome, and there is an urgent need to identify new management strategies.

Table 2. Clinical classification of pulmonary hypertension.

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 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
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 veins stenosis hypertension due to lung disease
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenosis
4.2.5 Parasites (hydatidosis)
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
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
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Others

Group 4

Group 4 includes patients with CTEPH and other conditions causing obstruction of the pulmonary arteries (*e.g.* angiosarcoma, intravascular tumors, arteritis, congenital pulmonary artery stenosis).[9] CTEPH is a rare and insidious complication of pulmonary embolism, due to unresolved, organised pulmonary artery thrombi. It is often diagnosed late and often occurs in patients with no history of symptomatic venous thromboembolism.

A V/Q scan to exclude CTEPH is recommended for all PH patients at the time of referral to a specialist centre. The treatment of choice is pulmonary endarterectomy (PEA), effectively lowering the pulmonary vascular resistance and significantly improving outcome. However, surgery is not possible in around a third of cases, who may benefit from PAH therapy or balloon pulmonary angioplasty.[10-12]

Group 5

Group 5 includes PH of unclear and/or multifactorial mechanisms (Table 2) and will not be discussed in this paper.

Diagnostic algorithm

Dyspnoea, syncope on effort, angina and fatigue, with progressive limitation of exercise capacity are typical symptoms related to PH, but lack specificity, as they are common in other cardiovascular and respiratory disorders. Therefore, clinical suspicion and awareness of PH is important in triggering investigations and avoiding misdiagnosis, or a delays in diagnosis, which is unfortunately still very common (see patient pathway, Figure 1, initial steps are characterised by misdiagnosis, causing anger, frustration and confusion to the patient, http://www.phauk.org/).[13] Indeed, it is typical for PH patients to have met several physicians regarding their symptoms, before a diagnosis of PH is made. Once the suspicion of PH is raised, the diagnostic algorithm provided by international guidelines should be followed.

Transthoracic echocardiography is key for screening patients and establishing a firm clinical suspicion of PH.[14] Echocardiography is widely available, cheap and easy to perform, but requires expertise in interpreting potential signs of PH. Continuous wave Doppler measurement of peak tricuspid regurgitation velocity is recommended for assessing the probability of PH (Figure 2). To estimate systolic PA pressure (in the absence of pulmonary stenosis), one has to add right atrial pressure (RAP) to the tricuspid regurgitation pressure gradient. Sources of error derive from insufficient, poorly recorded tricuspid regurgitation Doppler signals and inaccurate estimation of RAP.[15] Consequently, several additional echocardiographic signs have been proposed and should be sought, which relate to ventricles, the pulmonary artery, inferior vena cava and right atrium

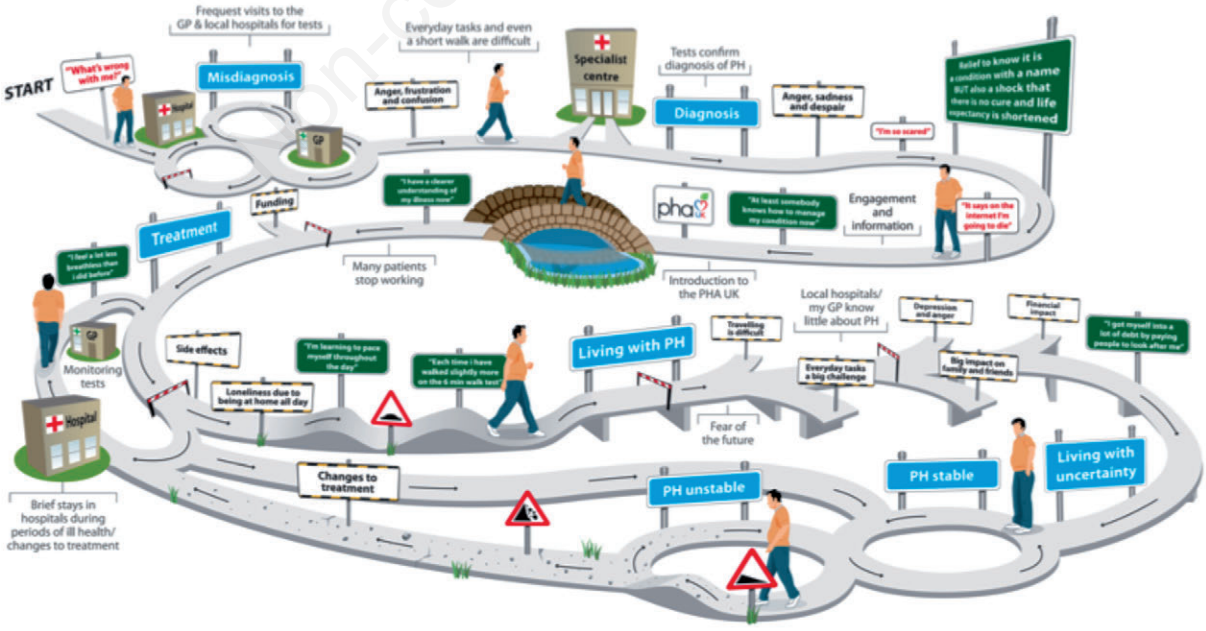
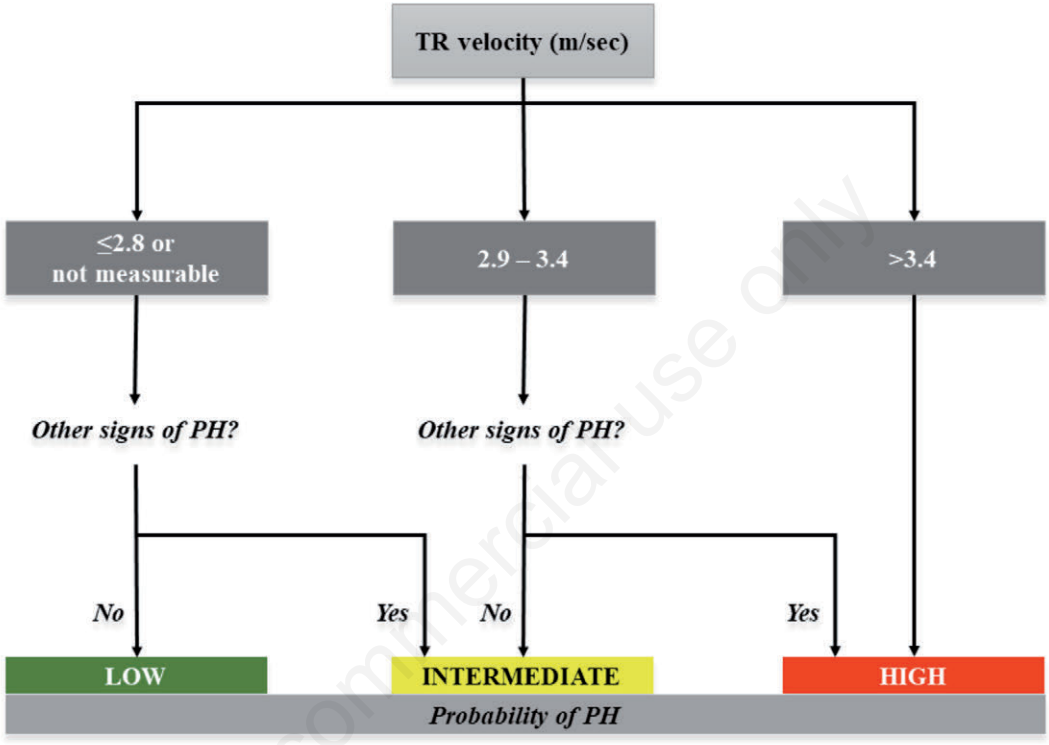


Figure 1. The pathway of the patient living with pulmonary hypertension (PH): from onset of symptoms, to diagnosis and treatment (http://www.phauk.org/).

(Figure 2).[1] Expertise is required when assessing patients with congenital heart disease, in whom the above signs may not apply.[16]

The diagnostic algorithm suggests that, when there is a low probability of PH on transthoracic echocardiography, no additional investigations are required and other causes for the symptoms should be considered (Figure 3). In patients with high or intermediate PH probability, further investigations are required, starting with the identification of patients with coexisting left heart disease or lung disease that are unlikely to be candidates for PAH therapies, but may benefit from expert review when signs of severe PH and RV dysfunction are present. Patients without



Other signs of PH

A The ventricles	B Pulmonary artery	C Inferior vena cava and right atrium
RV/LV basal diameter ratio >1.0	RV outflow Doppler acceleration time <105 ms and/or mid-systolic notching	IVC dimension >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the IVS (LV eccentricity index >1.1 in systole and/or diastole)	Early diastolic PR velocity >2.2 m/s	RA area (end-systole) >18 cm^2
PA dimension >25 mm		

Figure 2. The probability of pulmonary hypertension (PH) based on echocardiography: tricuspid regurgitation (TR) velocity and other signs of PH. RV/LV, right ventricle/left ventricle; IVC, inferior vena cava; IVS, interventricular septum; PR, pulmonary regurgitation; RA, right atrium; PA, pulmonary artery.

left heart or significant lung disease, should be referred to a recognised high-volume expert PH centre for further investigations, starting with a V/Q scan to identify CTEPH patients who may be candidates for PEA. Several other investigations are recommended to identify potential causes for PH, but the mainstay for establishing the diagnosis is cardiac catheterisation.[1]

The PH guidelines recommend that expert PH centres should care for at least 50 patients on PAH treatment, with at least two new PAH or CTEPH referrals per month. However, higher volumes and a wide diagnostic case-mix, with expertise in the use of all types of PAH therapies and a multidisciplinary approach to PH is advisable. PAH and CTEPH patients should be followed regularly in an expert centre, using multiple parameters for estimating risk, detecting disease progression and assessing the response to treatment.[17]

Risk stratification in pulmonary arterial hypertension patients

Risk stratification is part of the initial assessment and follow-up of PAH and CTEPH patients and is based on multiple clinical parameters, including functional variables, imaging and hemodynamic status.[1] For PAH patients, a risk stratification tool is proposed, based on estimated 1-year mortality from registry data (Table 3). Indeed, large contemporary PH registries have provided valuable information of risk stratification. These include the US-based Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) and the French Pulmonary Hypertension Network Registry (FPHN).[18,19] The REVEAL registry is a longitudinal registry, which has highlighted the importance of developing and validating multifactorial risk assessment tools. The FPHN was used to develop the French risk equation estimating survival at 3 years from diagnosis. The FPHN data was also used to estimate survival in patients with dual oral combination therapy. Notably, the expected survival of patients on initial dual oral combination therapy, using the French registry risk equation, was 97% at 1 year compared with the calculated expected survival rates of 86%.[20] Recently, Boucly *et al.* demonstrated that using a simple score by enumerating low-risk criteria present at diagnosis and after treatment initiation, was able to predict long-term transplant-free survival. Outcome was best in patients with >2 of the following: New York Heart Association (or the PH-specific World Heart Organisation) functional class I or II, 6-min walking distance >440 m, right atrial pressure <8 mmHg and cardiac index ≥2.5 L/min/m^2). The score also worked well when replacing invasive parameters with brain natriuretic.[21] The Prospective Registry of Newly

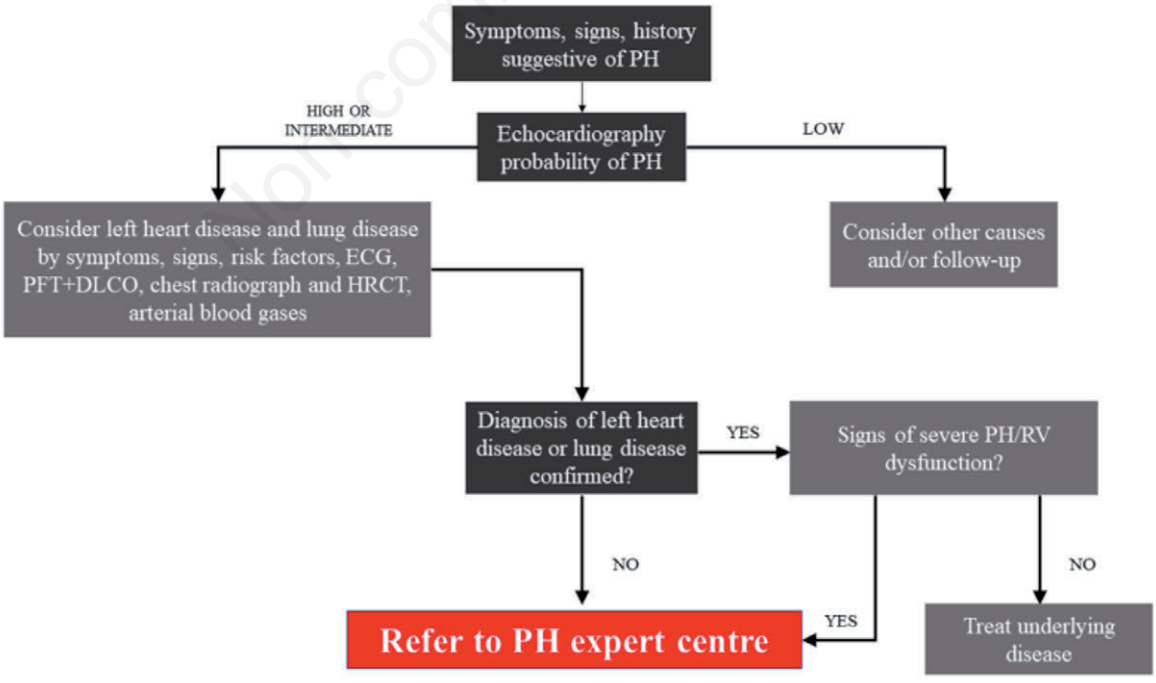


Figure 3. Diagnostic algorithm, according to the current pulmonary hypertension (PH) guidelines. ECG, electrocardiogram; PFT+DLCO, pulmonary function test+diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution computed tomography; RV, right ventricular.

Initiated Therapies for Pulmonary Hypertension (COMPERA) also confirmed that an abbreviated version of the risk assessment strategy proposed by the PH guidelines is accurate in estimating mortality in patients with PAH.[22]

Risk stratification tools should always be combined with clinical judgment by the PH expert, striving to achieve the lowest possible risk status, through aggressive management of the disease. PH guidelines recommend initial combination therapy in high risk patients, and initial oral monotherapy or combination therapy for low or intermediate risk patients.[1,21] Those at very high risk should be considered for prostanoid therapy.

Therapy

Pulmonary arterial hypertension

All forms of PAH share a common pathophysiology, characterized by endothelial dysfunction, abnormal intimal and smooth muscle proliferation and reduced apoptosis, resulting in elevated pulmonary pressures and right ventricular failure. Research in PAH has focused on identifying molecular targets for inducing vasodilation, inhibiting and reversing inflammation, proliferation, fibrotic changes and remodelling within the pulmonary vasculature. Currently used PAH therapies target one of the three major pathways involved in development and progression of PAH: the endothelin, the prostacyclin and the nitric oxide pathways (Figure 4). Most randomized controlled trials have included iPAH and CTD PAH patients, with a limited number of HIV-related, drug-related and repaired CHD patients. While in the past initial drug monotherapy was recommended in treatment-naïve patients, there is recent evidence to support upfront or early sequential combination therapy, with 2 drugs acting on the nitric oxide and endothelin pathways.[1] The Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial was a double-blind, event-driven phase III randomized controlled trial designed to investigate the effects of long-term treatment with macitentan (endothelin receptor antagonist, ERA) compared with placebo in patients with PAH using a composite primary endpoint of morbidity and mortality.[23] It was the first long-term trial in PAH and the first trial to use a clinically relevant composite primary endpoint. It has provided robust evidence that combination therapy with macitentan and a

Table 3. Risk assessment in pulmonary arterial hypertension according with the current guidelines.

Determinants of prognosis (estimated 1-year mortality)	Low risk	Intermediate risk	High risk
Functional variables			
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
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 slope ≥45
Imaging			
Echocardiography and CMR	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
Haemodynamic status			
Right heart catheterization	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%
Biochemical			
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L

WHO, World Health Organization; 6MWD, 6-minute walking distance; CMR, cardiac magnetic resonance; RA, right atrium; RAP, right atrium pressure; CI, cardiac index.

phosphodiesterae-5 inhibitor (PDE-5i) is beneficial on the clinical outcome of PAH patients. The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial established the value of upfront combination therapy in treatment naïve patients. This study demonstrated that ambrisentan (an ERA) and tadalafil (a PDE-5i) reduced the risk of clinical failure events by 50%, with a significant improvement in 6MWT distance and NTproBNP.[24] These two recent trials established the role of upfront or early sequential combination therapy, as recommended in the guidelines.

Prostanoids, especially intravenous or subcutaneous compounds, are currently used as third-line treatment, unless the patient presents with advanced disease, in functional class IV. Until recently, only inhaled, intravenous or subcutaneous drugs acting on the prostacyclin pathway were available, and were associated with significant side-effects and discomfort related to the mode of administration (*e.g.* line infections, local pain, *etc*.). Selexipag, an oral selective prostacyclin receptor agonist, has recently become available and the benefits of double and triple combination therapy with an ERA and/or a PDE-5i, were recently reported in the Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) trial.[25] Selexipag reduced morbidity and mortality in this PAH population. GRIPHON was the first large randomized controlled trial to support the use of triple combination therapy in PAH, which may be considered in patients who fail to respond to dual combination therapy, patients presenting with advanced disease, and those referred to transplantation.

In patients with PAH-CHD, the strongest evidence on PAH therapy is for bosentan (an ERA) and tadalafil (a PDE-5i).[26,27] The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) study showed a significant improvement in hemodynamic and exercise capacity with bosentan, without adversely affecting systemic arterial oxygen saturations.[26] The recently concluded Effects of Macitentan on Exercise Capacity in Subjects With Eisenmenger Syndrome (MAESTRO) trial failed to demonstrate a significant improvement in 6MWT distance, even though an improvement in PVR and BNP was reported.[28]

Pulmonary hypertension management in other diagnostic subgroups

PAH therapies should not be used in patients with post-capillary PH (Group 2, left heart disease) and there is no evidence for those with lung disease (Group 3). Treatment of the underlying condition is strongly recommended (*e.g.* LV dysfunction, valve disease, sleep apnoea, long-term oxygen

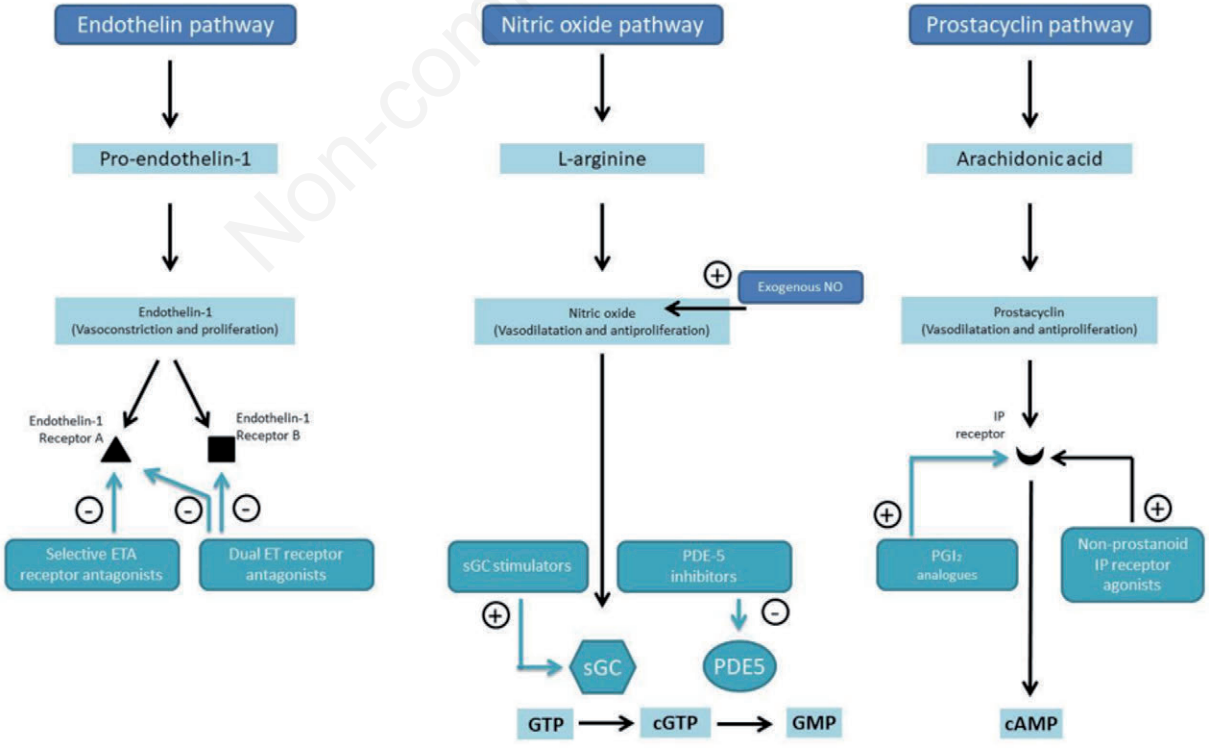


Figure 4. The three major pathways involved in the development and progression of pulmonary arterial hypertension.

supplementation in COPD) and is likely to improve the severity of PH. CTEPH is the only type of precapillary PH that can be cured through PEA in eligible patients. Indeed, referral of all CTEPH patients to a PEA centre at the time of diagnosis for advice on surgery is mandatory. Inoperable patients may benefit from balloon pulmonary angioplasty (Figure 5).

If patients are operable, PEA can lead to a substantial improvement in symptoms and a return to a normal life expectancy and quality of life. Inoperable patients or patients with an unacceptable surgical risk/benefit ratio or persistent PH after PEA, may be candidates for PAH therapy (most evidence for riociguat and macitentan, but PDE5-Is are often used).[29,30]

In the United Kingdom, the long-term survival post PEA at 10 years is 72% whereas patients who choose not to proceed to surgery, have a similar mortality to non-operable disease.[31] For this reason, it is important to obtain the opinion of an expert PEA team at diagnosis.

Quality of life in pulmonary hypertension

PH is a progressive debilitating condition that negatively affects patients' quality of life (QoL), by impacting on their ability to perform physically demanding everyday life activities: PH can affect their ability to work (whether in a physically active job or just commuting to work), their ability to play with or look after their children, maintain a healthy sexual relation and be socially active. Moreover, frequent follow-up appointments, repeat hospitalisations and laborious treatments with important side-effects (*e.g.* prostanoids, need for long-term oxygen) can have a psychological impact on patients with PH; regular assessment of QoL is as important as assessing exercise capacity or hemodynamics.

There are currently 2 disease (PH)-specific questionnaires: the Cambridge Pulmonary Hypertension Outcome Survey (CAMPHOR) score has been used for several year and addresses several aspects of the disease, but is quite lengthy (65 items), which limits its use in routine clinical practice.[32] A 10-question QoL questionnaire, called emPHasis 10 (E10), was recently designed specifically for use in routine clinical practice.[33,34] It was derived from three previous PH scores: the Minnesota Living with Heart Failure Questionnaire (MLHFQ) modified for PH, the Dyspnoea-12 (D-12) that reflects the physical perception and emotional effects of dyspnoea, and the Hospital Anxiety and Depression scale (HAD), which addresses psychological distress.[34,35] Each of the 10 questions is scored in a semantic 6-point scale (from 0 to 5), for a total maximum score of 50. The E10 score is currently used in most centres in the UK and has been translated into several languages (Figure 6).

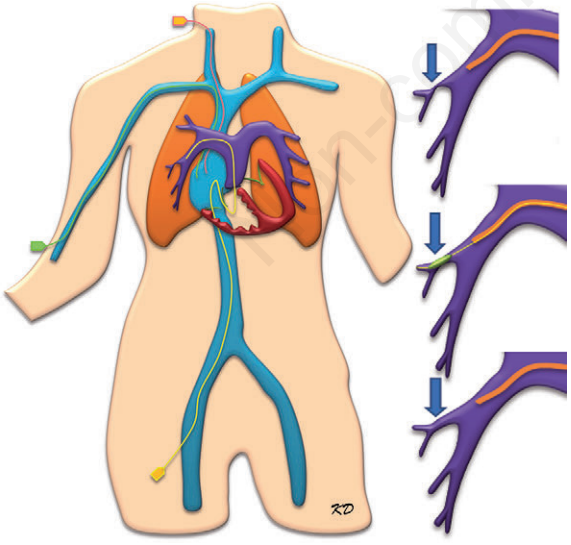


Figure 5. Balloon pulmonary angioplasty for chronic thromboembolic disease. Stenoses in peripheral vessels can be treated using balloon angioplasty: while no stenting is required, attention should be made to avoid vessel damage (and hemoptysis, which can be catastrophic) and reperfusion edema. For this reason, numerous procedures (average 3-4) are typically required, treating one segment each time.

The organisation of pulmonary hypertension care in United Kingdom and Ireland

In the UK and Ireland, a limited number of specialist centres have been designated as National Pulmonary Hypertension Centres, and are allowed to manage and prescribe PAH therapies, given the rarity of the disorder, its complexity and the cost of therapy.[1] There are currently 8 National PH Centres, working collaboratively to advise policy makers. PH centres are required to meet a strict set of standards for service delivery and are regularly inspected for compliance.

A multidisciplinary approach to PH is essential: the PH team should be composed of at least two senior physicians dedicated to PH, clinical nurse specialists, radiologists and cardiologists with expertise in PH imaging, echocardiography and RHC. PH centres should have access to several other services, including psychology, genetics, lung transplantation, adult CHD, high-risk anaesthetics and surgery, pregnancy and heart disease.

Each centre is expected to develop a network of *Shared Care* centres that allow management of patients closer to home, yet are responsible for ensuring high quality care, collecting data for the National PH audit, ensuring equitable access for patients and promoting

emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK pulmonary hypertension association

MANCHESTER 1824 The University of Manchester

Figure 6. The emPHasis10 score questionnaire. *Freely available from PHA-UK.*

education and research.[17] Shared care networks are important for facilitating access to specialist care across the country, reducing costs and discomfort relating to travel, especially in patients with significant disease. Moreover, patients are known to local services, that can contact the tertiary PH centre for advice when patients present decompensated, with an arrhythmia or other emergency.[36]

All designated centres in the UK are expected to manage at least 250 patients per annum with PAH or CTEPH. Participation in the National Audit is a legal requirement, allowing regular assessment of the services at National and local level, with regards to compliance with national standards.[1] The National Audit also provides epidemiological information for future planning, allocation of funds, and understanding the outcomes of patients with PH.[37,38]

Conclusions

PH is a progressive disease with a high mortality and mobility and should be part of the differential diagnosis of all patients presenting with dyspnoea and exercise intolerance of unclear cause. Prompt referral to specialist PH services is essential, ensuring rapid expert assessment and management for all patients. A limited number of National PH Centres, in proportion to the population, with a wider network of associated Shared Care PH centres, can result in an optimal balance of providing timely expert care as close to the patients' home as possible.

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