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ON THE DIAGNOSIS & MANAGEMENT OF
PULMONARY HYPERTENSION
2014 UPDATE

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The Taskforce of Pulmonary Hypertension Guidelines of the Saudi Association for Pulmonary Hypertension (SAPH)

Main guidelines

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Main Guidelines

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ABBREVIATIONS:

CI	Cardiac index
CO	Cardiac output
CHD	Congenital heart diseases
CHD-APAH	Pulmonary arterial hypertension associated with congenital heart disease
CPT	Cardiopulmonary exercise test
CTD	Connective tissue diseases
CTD-APAH	Pulmonary arterial hypertension associated with connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension
dPAP	Diastolic pulmonary arterial pressure
DPG	Diastolic pulmonary gradient
FC	Functional Classification
HR	Hazard Ratio
LVEDP	Left ventricular end diastolic pressure
NYHA	New York Heart Association
mPAP	Mean pulmonary artery pressure
$M\underline{V}O_2\%$	Mixed venous oxygen saturation
NT-pro BNP	N terminal-pro brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PH	Pulmonary hypertension
PPAH	Portopulmonary hypertension
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RHC	Right heart catheterization
RVEDP	Right ventricular end diastolic pressure
RVSP	Right ventricular systolic pressure
6MWT	Six minute walk test
sPAP	Systolic pulmonary artery pressure
SSc	Systemic sclerosis
SVR	Systemic vascular resistance
TAPSE	Tricuspid annulus plain systolic excursion
TPG	Trans-pulmonary gradient
TR	Tricuspid regurgitation
TRV	Tricuspid regurgitation jet velocity
TTE	Transthoracic Doppler-echocardiography
UA	Uric Acid
V/Q	Ventilation-perfusion

INTRODUCTION:

The Saudi Association for Pulmonary Hypertension (previously called The Saudi Association for Pulmonary Hypertension) has published the first Saudi Guidelines on Diagnosis and Treatment of Pulmonary Arterial Hypertension back in 2008.[1] That guideline was very detailed and extensive and reviewed most aspects of pulmonary hypertension (PH). One of the disadvantages of such detailed guidelines is the difficulty that some of the readers who just want to get a quick guidance or looking for a specific piece of information might face.

Thus, the taskforce for creating the 2014 updated guidelines has decided to write the new guidelines in two separate parts or sections. The first part is relatively brief and up-to-date, which is designed to give specific recommendations on general diagnostic and therapeutic algorithms. The second part, however, is more extensive and targets certain groups/diseases of pulmonary hypertension, such as connective tissue disease associated with pulmonary arterial hypertension (CTD-APAH), hemolytic anemia associated with PH, portopulmonary arterial hypertension (PPAH), congenital heart diseases associated with PAH (CHD-APAH), chronic thromboembolic pulmonary hypertension (CTEPH), creating detailed review articles. The second part will also include topics concerning updates on right ventricular disease in scleroderma, lung transplantation and other related topics. The panel reviewed several existing global guidelines for the management of PH. Local and international literature citations were reviewed and the final manuscript was reviewed by independent external auditors.

All efforts were made to develop this guideline in an easy-to-read form, making it very handy and helpful to clinicians dealing with PH patients to select the best management strategies for the typical patient suffering from a specific condition. This Guideline was designed to provide recommendations for frequent problems frequently encountered by practicing clinicians involved in management of PH. This publication targets mainly adult and pediatric PH-treating physicians, but can also be used by other physicians interested in PH.

It is important to emphasize that guidelines are not meant to substitute for clinicians' experience or detailed textbook knowledge, neither it is necessary appropriate to use a direct general recommendation from the guidelines towards a specific patient's presentation.

Finally, the European Society of Cardiology level of evidence and the class of recommendation were adopted for a particular diagnostic workup and for treatment options, as outlined in Tables 1 and 2.[2] Expert opinion or unpublished data are used only when necessary in the absence of adequate research and this is indicated in the text.

Table 1: Classes of recommendation

Class I	Good evidence/recommendation that a given treatment is effective
Class II *Class IIa* *Class IIb*	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment Weight of evidence/opinion is in favor of usefulness/efficacy; Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment is not useful or effective, and in some cases may be harmful.

Table 2: Levels of evidence for efficacy:

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 nonrandomized studies
Level of Evidence C	Data derived from small studies, retrospective studies, registries
Level of Evidence D	Consensus of opinion of the experts

DEFINITION:

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological state and not a disease per se. It can be found in multiple clinical conditions that may or may not share similar histological and pathophysiological abnormalities.

PH is defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest as assessed by right heart catheterization (RHC).[3,4] Because the normal mPAP is less than 20 mmHg, the significance of mPAP value between 21-24 mmHg is unclear at this stage, but may necessitate close follow up, especially in high-risk groups, such as systemic sclerosis or in the presence of a family history of PH ***(Level of evidence: C)***.

Other hemodynamic values such as pulmonary vascular resistance (PVR), pulmonary artery wedge pressure (PAWP), or cardiac output (CO) are not part of the definition of PH. However, PVR and PAWP should be included in the hemodynamic characterization of patients with pulmonary arterial hypertension (PAH) as follows: patients with PAH have pre-capillary PH (see below) characterized by mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, and elevated PVR [>3 WU].

The definition of PH in exercise as mPAP > 30 mmHg was mentioned in our previous guidelines.[1] However, this definition of PH is not supported by relevant data and should not be used for the time being.[5]

PREVALENCE:

While PAH is still considered as a rare disease, it is being increasingly recognized. Recent large multicenter registries have provided an estimate of PAH prevalence of 15-50 cases/million and incidence of 2.4 cases/million.[6-13] The age and gender distribution of the disease have evolved over time. The mean age of PAH patients at diagnosis is between 50 (±14) and 65 (±15) years in current registries, which is much older than the earlier NIH registry. Furthermore, the female predominance has found to be quite variable among different registries. While the French registry confirmed the female to male ratio of 1.6,[12] the US registry reported a much higher female preponderance of 3.9.[14] Such female predominance has been found to be less obvious in elderly patients.[15] A recent publication from Saudi Arabia aimed to report cases of PH and to compare the demographic and clinical characteristics of PH due to various causes has found that the mean age at diagnosis was 55.8 (±15.8) years and there was a female preponderance of 72.3%.[16]

CLINICAL CLASSIFICATION:

As per the 5th PH World Congress, PH continues to be classified into 5 groups according to pathological, pathobiological, and therapeutic characteristics (Table 3).[17] It is very important to categorize the patients within the right group, as approaches to therapy and management strategy vary significantly between different groups.

Table 3, Updated clinical classification of pulmonary hypertension (5th WORLD CONGRESS: Nice 2013)

Group 1: Pulmonary arterial hypertension (PAH)

- **1.1 Idiopathic**
- **1.2 Heritable**
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3 Unknown
- **1.3 Drugs and toxins induced**
- **1.4 Associated with (APAH)**
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases
  - 1.4.5 Schistosomiasis

Group 1': Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

Group 1": Persistent pulmonary hypertension of the newborn

Group 2: Pulmonary hypertension due to left heart disease

- **2.1 Systolic dysfunction**
- **2.2 Diastolic dysfunction**
- **2.3 Valvular disease**
- **2.4 Congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies**

Table 3, Updated clinical classification of pulmonary hypertension (5th WORLD CONGRESS: Nice 2013) Cont...

Group 3: Pulmonary hypertension due to lung diseases and/or hypoxemia **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 abnormalities**
Group 4: Chronic thromboembolic pulmonary hypertension
Group 5: Pulmonary hypertension with unclear and/or multifactorial mechanisms **5.1 Hematological disorders:** 5.1.1 Chronic hemolytic anemia 5.1.2 Myeloproliferative disorders 5.1.3 Splenectomy **5.2 Systemic disorders:** 5.2.1 Sarcoidosis 5.2.2 Pulmonary Langerhans cell histiocytosis 5.2.3 Lymphangioleiomyomatosis 5.2.4 Neurofibromatosis 5.2.5 Vasculitis **5.3 Metabolic disorders:** 5.3.1 Glycogen storage disease 5.3.2 Gaucher disease 5.3.3 Thyroid disorders **5.4 Others:** 5.4.1 Tumoural obstruction 5.4.2 Fibrosing mediastinitis 5.4.3 Chronic renal failure on dialysis 5.4.4 Segmental PH (Pediatric classification)

Table 4. Hemodynamic classification of pulmonary hypertension

Definition	Characteristics *(Based on right heart catheterization)*	Clinical group
Precapillary	• *mPAP ≥ 25 mmHg* • *PAWP (or LVEDP) ≤ 15 mmHg*	*I, III, IV, V*
Postcapillary	• *mPAP ≥ 25 mmHg* • *PAWP (or LVEDP) > 15 mmHg* ○ *Post-capillary PH: TPG ≤ 12 mmHg or DPG < 7 mmHg* ○ *Combined post & pre-capillary PH: TPG > 12 mmHg or DPG ≥ 7 mmHg*	*II*

TPG (Trans-pulmonary gradient) = mPAP – PAWP
DPG (Diastolic pulmonary gradient) = dPAP – PAWP

Hemodynamically, PH is classified into 2 groups; precapillary and postcapillary (table 4). Precapillary PH presents in clinical group I, III, IV & V, while postcapillary (also called venous pulmonary hypertension) presents in clinical group II.

Clinical Pearls:

- *Transpulmonary gradient (TPG) ≤ 12 mmHg indicates that PH is post capillary (pulmonary venous) hypertension and is caused by elevated left atrial pressure. Treatment of PH is not usually required, and therapy should be directed toward treating left ventricular or valvular dysfunction.*
- *TPG > 12 mmHg indicates combined precapillary and post-capillary components (formerly known as "out of proportion"). Therapy might be needed to address both venous and arterial sides.*
- *Recent evidence suggests that using the diastolic pulmonary gradient (DPG) rather than TPG is more accurate and physiological, as TPG might be influenced and affected by CO.[18] Value < 7 indicates post capillary PH, while value ≥ 7 indicates combined precapillary and post-capillary component.*

WHO CLINICAL GROUPS OF PULMONARY HYPERTENSION:

Group 1; Pulmonary Arterial Hypertension (PAH):

It is well recognizable that PAH has a complex multifactorial pathobiology that involves both biochemical pathways and cell types.[19,20] The increase in PVR is related to vasoconstriction[21] and uninhibited proliferation of different cells presumably resulting from impared apoptosis,[22] including endothelial cells, smooth muscle cells, and fibroblasts leading to obstructive remodeling of the pulmonary vessel wall (plexiform lesions). Inflammatory response and thrombosis are also present.[18] Endothelial dysfunction leads to impaired production of vasodilators and antiproliferative agents, such as NO and prostacyclin, along with overexpression of many vasoconstrictors and mitogenic substances such as thromboxane A2, endothelin-1, and growth factors.[21,23]

Detailed discussions of specific diseases [genetic-related (Heritable) PAH (HPAH), congenital heart disease associated with PAH (CHD-APAH), connective tissue disease associated with PAH (CTD-APAH), and Schistosoma-associated PAH) are presented later in this issue of the Journal as separate topics.

Group 2; PH due to left heart disease:

The mechanism of PH in group 2 patients is related to the passive backflow transmission of the high pulmonary venous pressure secondary to elevated left atrial pressure (LAP) and/or left ventricular end diastolic pressure (LEVDP). In these cases the trans-pulmonary pressure gradient (TPG) and/or the diastolic pulmonary gradient (DPG) are within the normal range (Table 4).

Detailed discussion of group 2 diseases is presented later in this issue of the Journal as a separate topic.

Group 3; PH due to lung diseases and/or hypoxemia:

The pathobiological mechanisms involved in group 3 diseases are many and include hypoxic vasoconstriction, inflammation, mechanical stress related to hyper-inflated lungs, and loss of capillaries.[24,25] Direct toxic effect of inspired toxin such as cigarette smoke has also been suggested.

Detailed discussion of group 3 diseases is presented later in this issue of the Journal as a separate topic.

Group 4; Chronic thromboembolic pulmonary hypertension (CTEPH):

Chronic thromboembolic pulmonary hypertension may complicate acute pulmonary embolism in 1-5% of cases.[26] Non-resolution of acute embolic material leading to mechanical obstruction of pulmonary arteries is the most important pathobiological process in CTEPH. Other processes include in-situ thrombosis, endothelial cell dysfunction, neuro-hormonal mediators release causing bilateral vasoconstriction, inflammation, platelets dysfunction, and other pro-coagulant abnormalities.[27,28] The plasma level of factor VIII, a protein associated with both primary and recurrent venous thromboembolism, is found to be significantly elevated in patients with CTEPH.[29]

Detailed discussion of group 4 diseases is presented later in this issue as a separate topic.

Group 5; PH with unclear and/or multifactorial mechanisms:

The pathobiology in this group is multifactorial.

CLINICAL APPROACH TO PULMONARY HYPERTENSION:

PH is rarely picked up in a routine medical examination and even in its later stages, the signs of the disease are nonspecific and can be easily confused with other cardiac or pulmonary conditions. In the recent REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) registry, 21% of patients had symptoms for more than 2 years before diagnosis.[30,31] Furthermore, in the French registry,[30] 75% of the newly diagnosed patients were in modified New York Heart Association (NYHA) functional class III or IV, (table 5). Similarly, in a regional registry from one center in Saudi Arabia,[32] 73% of patients were in functional class III or IV at the time of diagnosis. The modified NYHA functional classes are summarized in table 5.

Table 5. Definition of modified New York Heart Association functional class

Modified New York Functional Class	Definition
Functional class I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or pre-syncope.
Functional class III	Patients with pulmonary hypertension who have mild limitation of usual physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain or pre-syncope.
Functional class III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain or pre-syncope.
Functional class IV	Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Because of the substantial evidence that early detection of the disease improves the outcome,[33] annual screening for selected high-risk patients is recommended. Such risk includes patients with systemic sclerosis (SSc)[34] and those with a family history of PAH ***(Class of Recommendation: IIa)***. Other conditions, such as portal hypertension, might also warrant screening ***(Class of Recommendation is: IIb)***. The DETECT (Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis) study has evaluated a 2-step screening approach in patients with SSc with DLco 60% and disease duration of more than 3 years.[35] The first step used a simple screening test, including the presence of telangiectasia, anticentromere antibodies, right- axis deviation on electrocardiogram, and low diffusion capacity for carbon monoxide (DLco) and serum biomarkers (urate and N-terminal pro–B-type natriuretic peptide [NT-proBNP]). Step 2 included echocardiography in patients at risk followed by RHC. With this screening algorithm, the number of missed PAH cases was found to be only 4%.

Transthoracic echocardiography (TTE) is the most popular screening test for PH,[36] and should be the first test to be done once the disease is suspected clinically. Tricuspid regurgitation jet velocity (TRV) is used to estimate the right ventricular systolic pressure (RVSP) that should be equal to systolic PAP (sPAP) in the absence of pulmonary outflow obstruction. Table 6 illustrates the usefulness of TTE in the initial screening of PH.

Table 6, Echocardiographic criteria for the initial screening of high-risk patients for pulmonary hypertension

Likelihood for PH	Criteria	Level of Evidence	Recommendations
PH unlikely	• TRV ≤ 2.8 m/s, and • sPAP ≤ 35 mmHg, and • No additional echocardiographic criteria for PH, and • Asymptomatic	B	• No further action • Consider annual screening
PH possible	***Criteria A*** • TRV ≤ 2.8 m/s, and • sPAP ≤ 35 mmHg, and • Presence of additional echocardiographic criteria for PH, or symptoms suggestive for PH ***Criteria B*** • TRV 2.9 - 3.4 m/s, or • sPAP 36 - 45 mmHg	C C	• Absence of symptoms and clinical risk factors, repeat echo in 3-6 months • Presence of symptoms or clinical risk factor (such as a family history or certain diseases/ condition associated with PAH), proceed to RHC
PH likely	• TRV > 3.4 m/s, or • sPAP > 45 mmHg	B	• Proceed to RHC

In this guideline, the clinical approach for PH will be divided into 3 sections:

- Initial diagnostic workup
- Disease evaluation/clinical groups (based on clinical classification)
- Assessment of disease severity

1. INITIAL DIAGNOSTIC WORKUP:

a. Clinical diagnosis:

As mentioned, PH is rarely diagnosed on routine clinical assessment. However, the threshold of clinical suspicion should be lowered in subjects with conditions that predispose to PH, such as CTD or CHD. The physical signs in advanced cases are usually those of right heart failure/strain.

b. Transthoracic Doppler-echocardiography:

Transthoracic Doppler-echocardiography (TTE) is the first test to be done once the disease is suspected clinically. Beside the estimation of sPAP and TRV, TTE can also provide additional information about the cause and consequences of PH. This includes left ventricular dimensions and function, valvular abnormalities, left ventricular filling characteristics, right atrial size, inferior vena cava dimensions and pericardial effusion size.[37] Furthermore, shunt study with agitated saline should be obtained if intra-cardiac right-to-left shunting is suspected.

Important clinical pearl:

- *Despite the strong correlation of the TRV and TR pressure gradient, Doppler-derived pressure estimation may be inaccurate in the individual patient, hence the TTE should never be considered as the definitive diagnostic test for PH and should always be confirmed by RHC (Class of Recommendation: I).*
- *The performance and interpretation of TTE is highly user-dependent, and a great deal of experience is necessary in order to have confidence in the estimates of PAP and RV function (Class of Recommendation*: I).

c. Right heart catheterization:

RHC remains the gold standard diagnostic procedure, and is required in almost all situations. RHC is also important for prognostic hemodynamic measurements in this patient population.[38] Such parameters include right atrial pressure (RAP), mPAP, PAWP, CO by thermodilution (or by the Fick method in cases of systemic-to-pulmonary shunts), PVR, arterial and mixed venous oxygen saturation ($M\underline{V}O_2\%$), and superior and inferior vena cava oxygen saturation in cases of systemic-to-pulmonary shunts. As the assessment of PAWP is specifically important for the distinction between pre- and post-capillary PH, it is very important obtain accurate measurements. A number of common sources of inaccurate measurement should always be looked for and corrected; among

these are inaccurate leveling and zeroing of the system, over-wedging and under-wedging and respiratory variations. Therefore, accurate leveling should be obtained at the beginning of the procedure for each patient and after patient movement. The transducer level should be set at the level of mid-axillary line. Zeroing should be obtained after leveling by setting zero level at the atmospheric pressure. The operator should also ensure good quality wedge pressure waveform and set the pressure scale speed at a proper level for maximum visualization of pressure waves to allow accurate manual measurements. It has been shown that misclassification of PH using PAWP is a real problem and therefore, if there is any doubt in the accuracy of PAWP, then left ventricular end diastolic pressure (LVEDP) should be directly measured[39] ***(Class of Recommendation: I)***. Appendix 1 illustrates SAPH's RHC protocol.

Table 7 illustrates the different hemodynamic parameters that should be obtained by RHC.

Vasoreactivity, although it is not a part of the standard diagnostic workup, is very important to perform in selected patients because of its importance in disease evaluation and since it may influence treatment modality (see below).

The risks associated with RHC in patients with PH were evaluated in a multi-center, 5-year retrospective and 6-month prospective study.[40] A total of 7,218 RHC procedures were performed. The overall number of serious adverse events was 76 (1.1%).

The most frequent complications were related to venous access followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vasoreactivity testing. Four fatal events were recorded in association with any of the catheter procedures, resulting in an overall procedure-related mortality of 0.055%. However, despite the reported safety of the RHC, this procedure should only be performed in expert centers.

Important clinical pearls:

- *RHC is a must, not optional, for confirming and characterizing the diagnosis of PH (**Class of Recommendation: I**)*
- *RHC in PH patients is safe in experienced hands (**Class of Recommendation: I**)*
- *RHC should only be performed in centers staffed with experienced personnel in performing and interpreting RHC data (**Class of Recommendation: I**)*

- *Performing a full study with appropriate measurement of PAWP is crucial (**Class of Recommendation: I**)*
- *For PAWP, the zeroing level of the pressure transducer should be located at the mid-thoracic line in a supine patient halfway between the anterior sternum and the bed surface. This represents the level of the left atrium. The PAWP should be recorded as the mean of 3 measurements at end-expiration. (**Class of Recommendation: I**)*
- *LVEDP should be directly measured when there is any doubt about the accuracy of PAWP. (**Class of Recommendation: I**)*
- *LVEDP measurement should also be considered when PAWP is normal (<15 mmHg) in patients where there is high suspicion for left heart disease, e.g. hypertension, diabetes, enlarged left atrium, atrial fibrillation, or presence of coronary heart disease. (**Class of Recommendation: IIa**)* [41]

Table 7. Hemodynamic parameters measured during RHC

Parameter	Class of recommendation	Remarks
RAP	I	
CO/CI	IIa (see remarks)	By thermodilution (or by the Fick method in cases of systemic-to-pulmonary shunts)
M$\underline{V}O_2$%	IIa	
PVR	I	Needed for the diagnosis of PAH
mPAP	See remarks	For diagnostic purpose: Class of recommendation I For prognostic purpose: Class of recommendation IIb
PAWP	I (see remarks)	In case of inaccurate wedging, LVEDP should be measured
Vasoreactivity	See remarks	Class of recommendation I in IPAH Class of recommendation IIa in CHD-PAH and CTEPH Class of recommendation IIb in other forms of PH

2. DISEASE EVALUATION/CLINICAL GROUPS BASED ON WHO CLINICAL CLASSIFICATION (DIAGNOSTIC ALGORITHM):

The next step after confirming the diagnosis of PH is to identify the clinical group according to the WHO clinical classification (Table 3). Appendix 2 shows the SAPH protocol for a PH diagnostic algorithm

Pulmonary function tests (PFTs) and arterial blood gases (ABGs):
Class of recommendation: IIa

Pulmonary function test is an important initial investigation for all patients with PH in order to identify patients belonging to Group 3. However, 20% of PAH patients may have a mild restrictive defect.[42] DLco might also be reduced secondary to diminished pulmonary vascular volume and subsequent V/Q mismatch.[43] The degree of reduction in DLco in relation to vital capacity has shown a strong correlation with peak oxygen uptake, peak work rate, and modified NYHA class, but not with the degree of severity of PH itself.[44-46]

Ventilation and perfusion (V/Q) lung scan: *Class of recommendation to exclude CTEPH: I*
Because CTEPH is a potentially curable disease, it should be considered in all patients with unexplained PH. Ventilation-perfusion (V/Q) lung scan of patients with CTEPH generally shows one or more segmental-sized or larger mismatched perfusion defects.[42] A normal V/Q scan virtually excludes the diagnosis of CTEPH. However, false-positive scans may be seen with pulmonary artery sarcoma, large-vessel pulmonary vasculitis, extrinsic vascular compression, pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis.[47] The sensitivity of V/Q scanning ranges from 90 to 100% with specificity of 94 to 100%.[48,49]

CT Scan of the lung: *Class of recommendation to exclude CTEPH: IIb*
Chest CT scan is an important test in the evaluation of PH. High resolution CT scan (HRCT) provides help in confirming, or ruling out, the presence of certain diseases that could be responsible for the development of PH, such as interstitial lung diseases (ILD), emphysema, or bronchiectasis.[50] Pulmonary capillary hemangiomatosis is usually suspected by the presence of diffuse bilateral thickening of the interlobular septae and the presence of small centrilobular, poorly circumscribed, nodular opacities, and mediastinal lymphadenopathy.

The presence of interstitial markings similar to those seen with advanced left ventricular failure, diffuse central ground-glass opacification and thickening of interlobular septa, suggest pulmonary veno-occlusive disease.

The role of contrast-enhanced spiral CT in the evaluation of CTEPH is still evolving. For the time being, it cannot replace V/Q scan. Unilateral perfusion defects seen on contrast-enhanced spiral CT scan may suggest alternative diagnoses, such as sarcoma, vasculitis, malignancy, and mediastinal fibrosis.[51] Finally, CT may also be useful in determining the extent of small-vessel involvement and the likelihood of improvement after thromboendarterectomy.[52] CT pulmonary angiography should be considered to be a complementary test to the V/Q scan.

Pulmonary angiography: *Class of recommendation for surgical evaluation of CTEPH: IIa*
Despite the growing advantages of contrast-enhanced spiral CT, pulmonary angiography is still required by some surgeons in the workup of CTEPH, especially in those patients that are considered for pulmonary artery endarterectomy.[53] With the availability of new contrast agents and the use of selected views only, the pulmonary angiography has been shown to be safe in PH.[54] Pulmonary angiography can be part of the RHC but should be performed after all hemodynamic assessments have been performed.

Magnetic resonance imaging (MRI): *Class of recommendation: IIb*

MRI is a very promising tool for the evaluation of pathological changes in both the heart and the pulmonary circulation in PH patients.[55] However, at the current time, MRI has not been included in the standard diagnostic algorithm of PH.

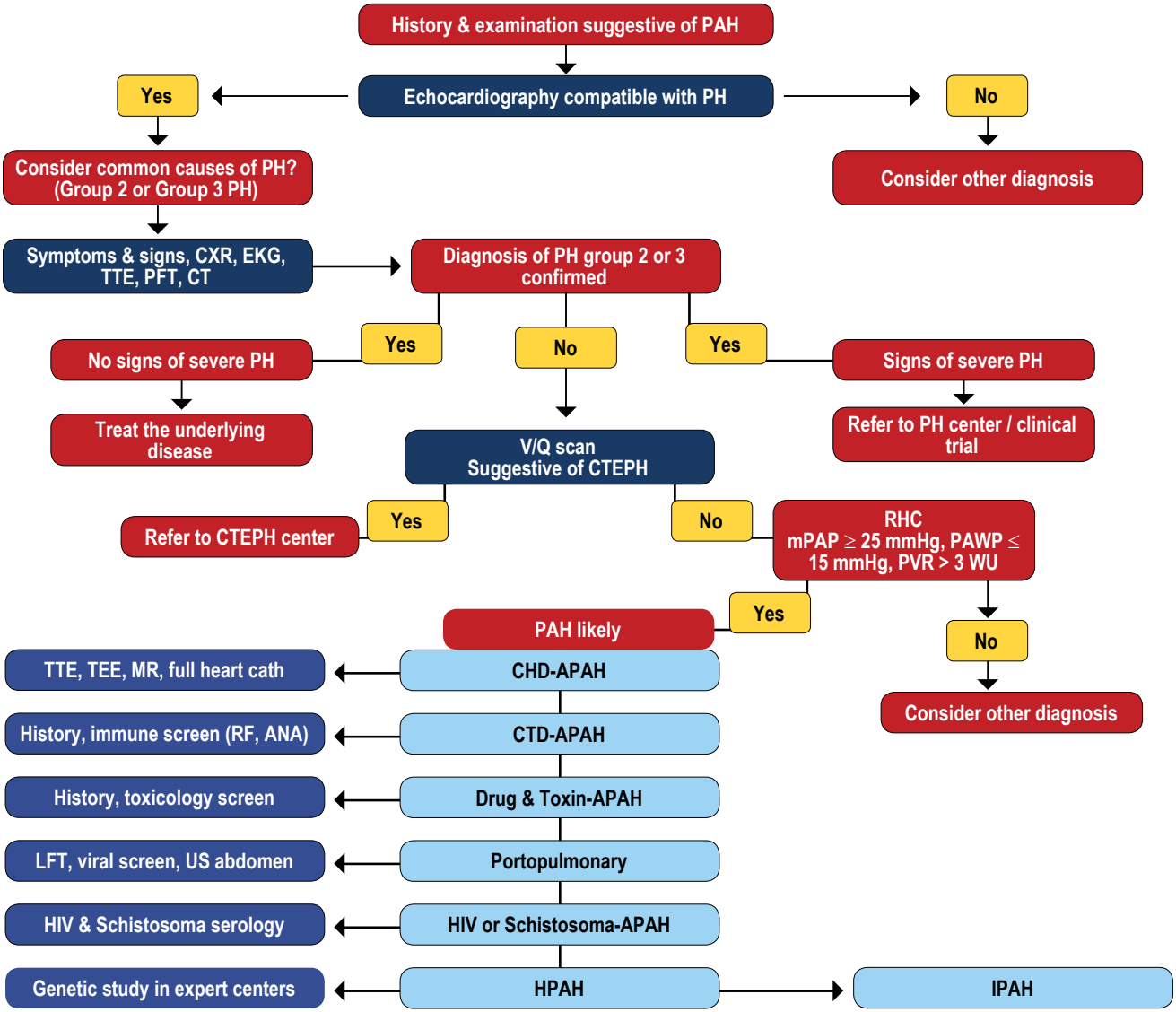
Lung biopsy: *Class of recommendation: III*

Open or thoracoscopic lung biopsy carries substantial risks of morbidity and mortality in PH patients and is not recommended in most situations.[56]

Other investigations: *Class of recommendation: I*

Testing for connective tissue diseases, hemoglobinopathy, HIV & schistosoma serology, thyroid function, hepatic ultrasound & viral hepatic screen, and liver and renal function tests:
Figure 1 illustrates the diagnostic algorithm in PH.

Figure 1: Evidence-based diagnostic algorithm of PH:



3. ASSESSMENT OF DISEASE SEVERITY AND PROGNOSTIC MARKERS:

When the diagnosis of PH is confirmed and the WHO clinical grouping has been determined, additional investigations may be required for assessment of disease severity, exercise capacity and hemodynamics. Several variables have been shown to predict prognosis in idiopathic pulmonary arterial hypertension (IPAH) when assessed at baseline or after specific treatment.[57] However, the significance of these prognostic variables is less clear when applied to other conditions such as PAH associated with CTD, congenital heart disease, HIV infection or portal hypertension.

Demographics:

Prognostic significance of demographic variables such as age and gender are inconsistent. In a retrospective study,[58] younger age at the time of diagnosis was associated with a worse prognosis when compared to older patients. On the contrary, another study that included patients with many etiologies of PAH who were treated with epoprostenol, older age at diagnosis indicated a worse prognosis.[59] Such findings, however, may be affected by including patients with the scleroderma spectrum of disease, who tend to be older and also had a worse prognosis.

Many recent registries have reported a worse outcome in incidence cases (patients with new diagnosis of PH) compared to prevalence cases (patients who have previously received the diagnosis). However, this should be taken with extreme caution, as the survival from time of enrollment in prevalent cases can lead to biased results if generalized to incidence patients, while survival from the time of diagnosis can lead to biased estimates if those results are generalized to a group of prevalent patients.

Modified NYHA Functional status:

Baseline modified NYHA functional classification (FC) has a definite prognostic predictive value in patients with IPAH.[38] This predictive value is consistent even when NYHA classification is assessed either before or 3 months after the initiation of epoprostenol treatment.[60,61] Such functional classification should be always considered in managing patients with PH. Patients presented with right heart failure before the initiation of treatment have a worse prognosis.[61]

Exercise tolerance:

Objective assessment of exercise tolerance in patients with PAH is an important tool for evaluating disease severity,[61-63] disease outcome, and treatment effectiveness.[57,64] Six-minute walk test

(6MWT) and cardiopulmonary exercise test (CPET) are the most commonly used tests for this purpose and traditionally have been widely used as the primary endpoint in older studies. Recent studies, however, are tending to use a composite endpoint (clinical worsening, combined morbidity/mortality) as the primary endpoint.

Six-MWT has to be validated in any site using it for clinical care and/or clinical trials. As the name implies, it measures the walking distance covered in 6 minutes walk.[65] It is usually combined with the Borg dyspnea score for the subjective assessment of the level of dyspnea with the exercise. It is important to realize that although the absolute 6MWT distance (i,e, > 380 - 440 m) has prognostic implications, a change in 6MWT distance with therapy dose not necessary impact the prognosis.[62] Appendix 3 shows the SAPH 6MWT protocol.

CPET is a more complicated test compared to 6MWT. PH patients characteristically show reduced cardiac reserve as manifested by reduced peak oxygen consumption (VO_{2max}), reduced peak work rate, reduced anaerobic threshold, and reduced peak oxygen pulse indirectly reflecting low cardiac stroke volume.[66] VO_{2max} determined by CPET has been found to be an independent predictor of survival in patients with IPAH.[63] Patients with peak VO_{2max} of > 10.4 ml/kg/min have a better survival than those with lower VO_{2max} (91% vs 50%; p< 0.0001).[63] Finally, patients with a peak systolic blood pressure (SBP) > 120 mmHg during CPET were also shown to have a better 1-year survival than those patients who did not achieve this systolic pressure. For clinical purpose, it is been accepted that VO_{2max} <10 ml/min/kg indicates poor prognosis and a need to escalate treatment, while a level of >15 ml/min/kg indicates better prognosis.

Echocardiographic variables:

Echocardiographic indices that have been predictive of survival in many studies include the presence of a pericardial effusion (HR, 3.89) and RA area index (HR, 1.54).[37,67,68] RV index (Tei index) is also found a predictive variable, but it could be affected by loading conditions and degree of tricuspid regurgitation.[69,70] Tricuspid Annular Plane Systolic Excursion (TAPSE) has also been reported to be useful in assessing RV function and a TAPSE score of > 1.5 cm has been found to be associated with better survival in PAH patients.[71,72]

Finally, there is no consensus in defining the severity of PH as assessed by echocardiographic estimation of RV systolic pressure that correlates with RHC–derived parameters.

Hemodynamics prognostic variables:

Many hemodynamic parameters, which have both diagnostic and prognostic significance, can be obtained by RHC (see above under RHC). These parameters are illustrated in table 7. Baseline hemodynamic variables, although important, appear to have less prognostic value compared to post treatment measurements in IPAH patients.[73]

Acute vasodilator testing:

Acute vasodilator testing should be done in selected individuals using short acting pulmonary vasodilators.[74-77] Half-lives, dose ranges, and duration of administration for suggested agents are provided in Table 8.

The rationale for acute vasodilator testing is based on the concept of the presence of reversible vasoconstrictive component in some patients with PAH, probably indicating a specific phenotype of the disease. The presence of a vasodilator response indicates a potential target of treatment with smooth muscles vasodilators, such as calcium channel blockers (CCBs). Acute vasoreactive testing is the only method by which the identification of the reversible vasoconstrictive component is possible. Empiric therapy with CCBs in order to identify patients with reversible component might be detrimental and strongly prohibited ***(Class of Recommendation for empiric use of CCBs in PAH patients: III)***.[78]

A positive acute vasoreactive response (positive acute responders) is defined as a reduction of mPAP by >10 mmHg to reach an absolute value of mPAP < 40 mmHg, with an increase or unchanged cardiac output.[79,80] The incidence of the positive response in IPAH patients, who may be long-term responders to CCBs, is around 7-10%.[81]

IPAH patients, who are positive acute responders, have a very favorable prognosis and good response to CCBs.[17,82] The usefulness of acute vasoreactivity tests and long-term response to CCBs in patients with other PAH types is less clear. Recent data have suggested a favorable outcome in CHD-APAH and CTEPH patients showing positive acute response treated with modern targeted PH therapy (not CCBs).[83,84] No data are available on the usefulness of long-term CCBs therapy in PAH patients other than IPAH, or in non-PAH groups, and therefore the value of performing a vasoreactivity test in clinical groups 2,3,4, and 5 is questionable.

Table 8: Suggested agents used for acute pulmonary vasoreactivity tests

Drugs	Route	Half-life	Dose Range (*)	Initial dose	Increments (^)	Duration (Y)
Nitric Oxide	Inhaled	15-30 Sec	-	20-40 ppm	-	5 min
Adenosine (**)	IV	5-10 Sec	0.001 – 0.05 mg/kg/min	0.001 mg/kg/min	0.01 – 0.02 mg/kg/min	2 min
Inhaled Iloprost	Nebulized	10-20 min	-	5 mcg	-	15 min
Epoprostenol	IV	3 min	2-16 ng/kg/min	2 ng/kg/min	2 ng/kg/min	10 min

* : Initial dose and maximum dose suggested
^ : Increments of dose by each step
Y : Duration of administration on each step
** : Although adenosine is no longer recommended in international guidelines, adding it here reflects availability and ease of use in the cath labs in Saudi Arabia

Blood tests (prognostic biomarkers):

Brain natriuretic peptide (BNP) and NT-pro BNP levels are elevated in RV pressure overload and correlates with severity of the right ventricular dysfunction and mortality in PAH patients.[85] Increased uric acid (UA) level reflects impaired oxidative metabolism and serum UA level was also found to increase in proportion to the severity of the functional class and correlated with CO, PVR, and $M\underline{V}O_2$.[86]

Detailed discussion of biochemical markers in the management of PAH is presented later in this issue of the Journal as a separate topic.

Clinical Pearls: Poor prognostic variables:

- *Modified NYHA functional class III or IV on optimal therapy (**Level of evidence: A**)*
- *Incident cases have poorer outcome compared to prevalent cases (**Level of Evidence: C**)*
- *Walking < 250 meter before the initiation of epoprostenol or < 380 meter after 3 months of epoprostenol treatment (**Level of evidence: B**)*
- *Low VO_{2max} (<10.4 ml/kg/min) & low peak exercise SBP (<120 mmHg) as determined by CPET: (**Level of evidence: B**)*
- *Echo: Pericardial effusion and low RV function (TAPSE < 1.5 cm): (**Level of evidence B**)*
- *Hemodynamics: High RAP and low CI/COP (**Level of evidence: A**)*
- *Negative vasoreactivity testing in IPAH (**Level of evidence B**)*
- *Elevated BNP or NT-pro BNP level (**Level of evidence: B**)*

TREATMENT:

Treatment of PH is challenging and the prognosis is still poor. We strongly recommend that PAH patients be referred to specialized centers for diagnosis and treatment. Appendix 4 illustrates the defining criteria for PH centers and the contact details of available PH agencies in the Kingdom of Saudi Arabia.

The management of PAH patients should not be considered simply as a mere prescription of drugs, as it is characterized by a complex strategy that requires serial evaluation of severity, supportive and general measures, deep understanding of invasive hemodynamic parameters, and the knowledge of estimation of drugs' efficacy and combination of different drugs and their interactions. In any of these steps, the knowledge and experience of the treating physician are crucial to optimize the patient outcome. PH patients should also be treated in a locale where they will have access to the full range of potential therapies.

The following discussion is intended to give only a brief review of treatment options and the proposed treatment algorithm. The reader may refer to the article entitles "*Treatment of Pulmonary Hypertension*" in this issue of the Journal for detailed discussion for each class of therapy.

The first step in managing PAH is to create a comprehensive treatment strategy based on variables with established prognostic significance (see above under Assessment of Disease Severity). Accordingly, the patient should be classified as falling in either the "*controlled/good prognosis*" group or the "*uncontrolled/poor prognosis*" group. Table 9 lists several parameters reflecting the criteria and parameters for these two prognostic groups.

Treatment decisions should be based on relevant prognostic parameters that reflect symptoms and exercise capacity. Recently, a goal-oriented strategy has been suggested as the best therapeutic strategy, in which pre-determined goals are considered as the treatment target.[87]

Serial evaluation of disease progression/control should be done on regular basis, usually 3-6 month intervals. Each evaluation should depend on a composite of data derived from clinical evaluation, exercise tests, biochemical markers, echocardiography and hemodynamic assessments.[61,88,89]

Table 9: Parameters of goal-oriented strategy

Controlled Good Prognosis	Prognostic Markers	Uncontrolled Poor Prognosis
I – II	Modified NYHA functional class	III – IV
No	Clinical evidence of heart failure	Yes
> 440 m VO_{2max} > 15 ml/kg/min & SBP > 120 mmHg	6MWT & Peak exercise (CPET)	< 380 m VO_{2max} < 10.4 ml/kg/min & SBP < 120 mmHg
Normal / near normal	Biochemical Markers (BNP & NT-Pro BNP)	Abnormally high
No signs of RV failure, TAPSE > 2 cm No pericardial effusion	Echocardiography	Signs of RV failure/ dysfunction, TAPSE < 1.5 cm Pericardial effusion
RAP < 8 mmHg CI ≥ 2.5 - 3.0 L/min/m^2	Hemodynamics from RHC	RAP > 10 mmHg CI < 2.0 L/min/m^2

Modern therapy has clearly led to a significant improvement in patients' prognosis. A meta-analysis performed on 23 RCTs in PAH patients showed a 43% decrease in mortality and a 61% reduction in hospitalizations in patients treated with specific drug therapies compared to patients randomized to placebo.[90]

Tables 10 & 11 provide the level of evidence and the class of recommendation for each treatment profile.

Table 10: Class of recommendations and level of evidence for general measures and background therapy efficacy in PAH

Treatment	Level of Evidence			Class of Recommendations			Remarks
	A	B	C	FC II	FC III	FC IV	
General measures			✓	I	I	I	
Oral anticoagulants			✓	IIa	IIa	IIa	In IPAH
			✓	IIb	IIb	IIb	In other PAH
Diuretics			✓	I	I	I	
Digoxin			✓	-	IIb	IIb	In patients with right-sided HF
Oxygen			✓	-	I	I	If arterial oxygen saturation is <90%
Supervised rehabilitation	✓			I	I	I	

Table 11: Class of recommendations and level of evidence for specific treatment measures efficacy in PAH

Treatment		Level of Evidence			Class of Recommendations			Remarks
		A	B	C	FC II	FC III	FC IV	
CCBs	**Calcium channels blockers**			✓	I	II	III	• *Should be used ONLY in vasoreactive patients* • *May be harmful in FC IV patients*
Prostacyclin	**Beraprost**		✓		IIb	IIb	-	
	Epoprostenol	✓			-	I	I	
	Iloprost (Inhaled)	✓			-	I	IIa	
	Iloprost (IV)			✓	-	IIa	IIa	
	Treprostinil (S/Q)		✓		-	I	IIa	
	Treprostinil (IV)			✓	-	IIa	IIa	
ERA	**Ambrisentan**	✓			I	I	IIa	
	Bosentan	✓			I	I	IIa	
	Macitentan	✓			I	I	IIa	
NO Pathway: *(PD-5 Inh. & sGC stimulator)*	**Sildenafil**	✓			I	I	IIa	
	Tadalafil	✓			I	I	IIa	
	Riociguat	✓			I	I	IIa	*Also in CTEPH*
TK inhibitors	**Imatinib**	✓			-	IIb	IIb	• *High rate of side-effects* • *Need further studies*
Combination strategy	**Upfront combination**			✓	-	IIb	IIb	
	Sequential combination	✓			-	I	I	
Surgical procedures	**Atrial septostomy**			✓	-	IIb	IIa	
	Lung transplantation			✓	-	-	I	

CCBs, calcium channel blockers; PGI_2-R, prostacyclin receptors; ERA, endothelin receptors antagonist; NO, Nitric oxide; PD-5 Inh., phosphodiesterase-5 inhibitors; sGC, soluble guanylate cyclase; TK, Tyrosine Kinase.

TREATMENT ALGORITHM:

The evidence-based treatment algorithm is shown in Figure 2. Because of the lack of head to head trials comparing different drugs, the drugs are listed based in alphabetical order within each group and not ordered based on efficacy.

The treatment algorithm is mainly applicable to patients in modified NYHA FC II, III, & IV because they represent the predominant population included in RCTs. For modified NYHA FC I patients, few data are available, and the most appropriate strategy has still to be determined by specific studies.

Modified NYHA FC II Patients:

Recent studies showed that early intervention of PAH patients with very minimal symptoms and good exercise tolerance is appropriate and beneficial.[91]
Modified NYHA FC II patients should be:

- Enrolled in a rehabilitation program.[92,93] (***Class of recommendation: I***)
- Treated with general supportive measures and with initiation of background therapy that includes oral anticoagulants[82,94] (only in IPAH and CTEPH patients) (***Class of recommendation: IIa***) and diuretics in case of fluid retention (***Class of Recommendation: I***). Supplemental oxygen is unlikely to be required at this stage, but should be considered in case of arterial hypoxemia.
- Acute positive vasodilator responders, should be treated with optimally tolerated dose of calcium channel blockers (CCBs).[17,82] (***Class of recommendation: I***). Maintenance of the response (controlled/good prognosis) should be confirmed after 3 to 6 months of treatment as well as long-term, as some patients may convert from vasoreactive to non-vasoreactive over time.[83,95] However, it should be emphasized that CCBs are contraindicated in patients with right-sided heart failure, even if they are vasoreactive (table 11).
- Non-vasoreactive patients should be treated by specific target therapy, including bosentan,[96] ambrisentan,[97] sildenafil,[98] and tadalafil[99] (***Level of evidence: A***). Beraprost sodium[100] has also been used and approved in Japan and many Asian countries (***Level of Evidence: B***). Newer drugs, macitentan[101] and riociguat,[102] may also be approved for FC II patients based on recently completed studies.

Modified NYHA FC III patients:

Modified NYHA FC II patients should be:

- Referred for lung transplant evaluation (***Class of recommendation: IIa***)
- Enrolled in a rehabilitation program (***Class of recommendation: I***)
- Treated with general supportive measures and background therapy (***Class of recommendation: I***)
- Acute positive vasodilator responders should be treated with optimally tolerated doses of CCBs (***Class of recommendation: I***); maintenance of the response (controlled/good prognosis) should be confirmed after 3 to 6 months of treatment. Long-term stability on CCBs therapy should always be monitored.
- Non-vasoreactive (or vasoreactive patients who remain in NYHA functional class III despite treatment with background therapy and CCBs) should be treated by specific target therapy (***Class of recommendation: I***).

  We recommend the following approach:

  i. Sildenafil 20 mg BID (***Level of Evidence A***), *or*
  ii. Tadalafil 40 mg daily (***Level of Evidence A***), *or*
  iii. Bosentan 62.5 mg orally bid for the first four weeks and then up titrate to the target dose of 125 mg BID (***Level of Evidence A***) (do serial liver function tests for liver toxicity and optimize contraception in young female), *or*
  iv. Start ambrisentan 5 mg OD (***Level of Evidence A***), *or*
  v. Start Inhaled Iloprost 1 ampule (2.5 - 5 mcg) Q 4 hourly (Level of Evidence A).
  vi. Macitentan and riociguat are not yet commercially available in Saudi Arabia. However, these 2 drugs have proven in randomized clinical trials to have added benefits and should be considered as first-line therapy once available.

The choice of drugs is dependent on a variety of factors, including the cost, availability status, route of administration, side effects profile, patient's preferences, and physician's experience.

Response to treatment should be evaluated in 3 months time:

a. If the patient shows favorable response (controlled/good prognostic criteria) then treatment should be continued with monotherapy by using 1 of the above-mentioned agents and monitored periodically in 3-6 months period. (***Class of recommendation: I***).

b. If the patient failed to show a favorable response, consider combination therapy. (***Class of recommendation: I***). The following combinations have been tested in RCTs (The reader may refer to the article of Specific treatment of pulmonary arterial hypertension in this issue of the Journal for detailed discussion for each class of therapy):
   i. Sildenafil plus inhaled iloprost[103]
   ii. Inhaled iloprost plus bosentan[104]
   iii. Sildenafil plus bosentan[105]
   iv. Tadalafil plus bosentan[106]
   v. Prostanoid plus sildenafil[107]
   vi. Triple combination therapy might also be considered (***Class of recommendation IIb***)

c. If the patient shows favorable response (controlled/good prognostic criteria) then treatment should continue with the combination therapy and monitored periodically in 3-6 months period.

d. If the patient fails to show a favorable response on combination therapy, one or all of the following should be considered:
   i. Start IV epoprostenol infusion.[108] (***Class of recommendation: I***). A starting dose of 2 ngm/kg/min is recommended. The dose can be increased gradually until the optimal dose is achieved or limiting side effects (headache, flushing, diarrhea, or leg pain) prevent further dose escalation.
   Most patients will tolerate an average dose of 20-40 ng/kg/min. However, optimal dose can vary significantly from one patient to another; in particular children require a much higher dose of epoprostenol for optimal response (i.e. 80 – 200 ng/kg/min), or
   ii. Start S/Q[109] (***Class of recommendation: I***) or IV[110] (Class of recommendation: IIa) treprostinil infusion. A starting dose of 1-2 ng/kg/min is recommended. The dose should be up titrated slowly, especially if there is an injection site pain. Most patients will tolerate an average dose of 20-40 ng/kg/min. or
   iii. Start IV iloprost infusion.[111] (***Class of recommendation: IIa***). A starting dose of 0.5 ng/kg/min is recommended. The dose can be increased slowly until the optimal dose is achieved or limited by side effects. Again, most patients will tolerate an average dose of 20-40 ng/kg/min.
   iv. Consider atrial septostomy.[112] (***Class of recommendation: IIb***)
   v. In selected individuals, refer the patient for lung transplantation assessment.[113] (***Class of recommendation: I***)

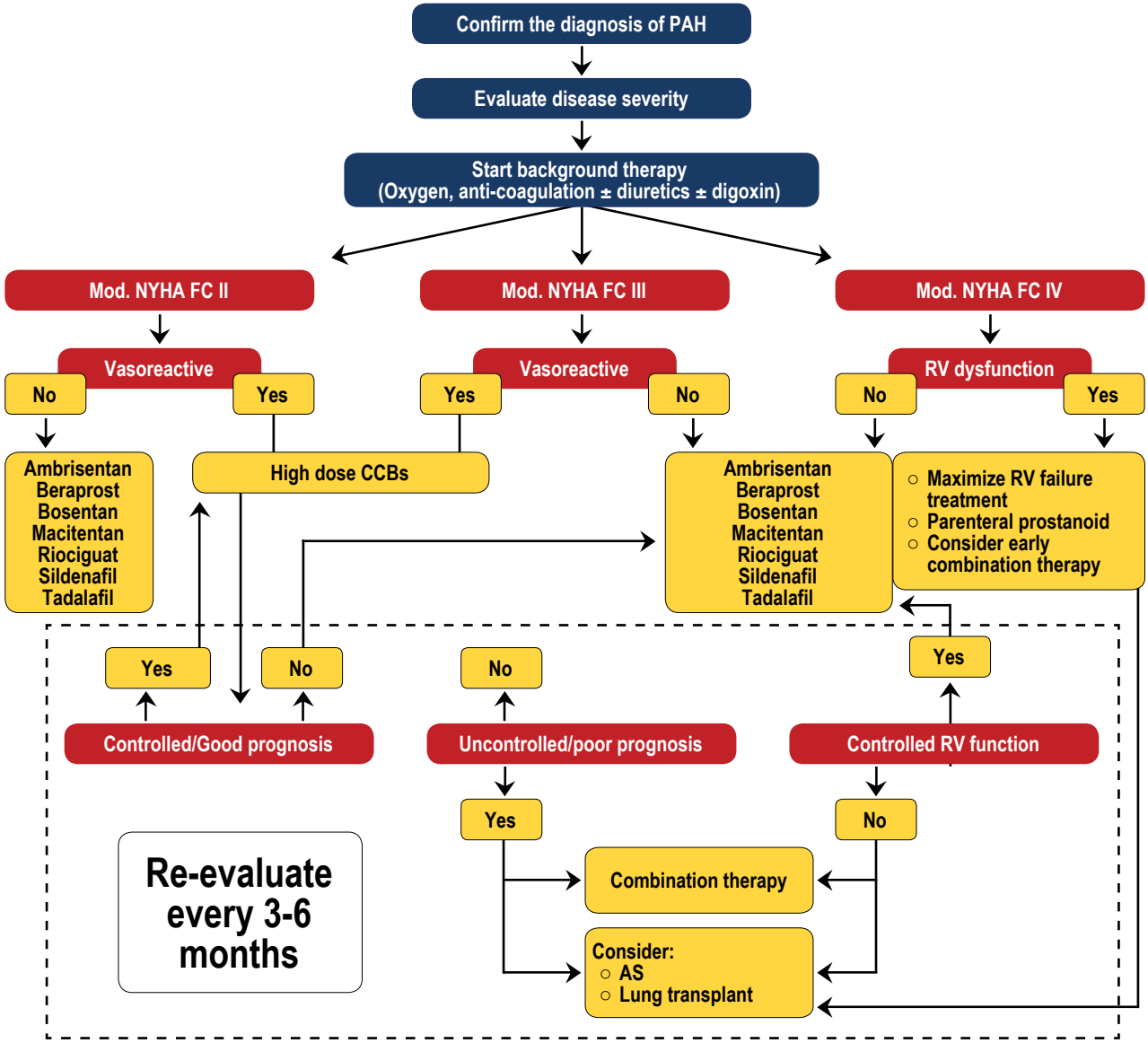
Modified NYHA FC IV patients:

All modified NYHA FC IV patients should be treated with the background therapy. (***Class of recommendation: I***) Modified NYHA FC IV patients do not need a vasoactive testing, as the management for those patients is guided in general by right ventricular status and not vasoreactivity. (***Class of recommendation for vasoreactive test in NYHA FC IV: III***)

Modified NYHA FC IV patients should be:

- Referred urgently for lung transplantation evaluation. (***Class of recommendation: I***)
- Referred to a rehabilitation program once stabilized. (***Class of recommendation: I***)
- Modified NYHA FC IV patients with *compensated* right ventricular function should be treated exactly as modified NYHA FC III, non-vasoreactive, patients. Despite the lack of good evidence and the high cost, sequential combination therapy with the drugs mentioned above should probably be considered early in the course of management. (Class of recommendation: I)
- Upfront combination therapy might be considered.[114,115] (***Class of recommendation: IIb***)
- Modified NYHA FC IV patients with decompensated RV should be treated by continuous IV epoprostenol infusion as first line therapy. (***Class of recommendation: I***)
- Atrial septostomy (***Class of recommendation: IIa***) and/or lung transplantation (***Class of recommendation: I***) are indicated for refractory patients, and specially those with recurrent syncope and/or right sided heart failure. These procedures should be performed only in experienced centers.

Figure 2: PAH, Evidence-based treatment algorithm



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Appendix 1: RHC & acute vasodilator protocol

Pulmonary Hypertension

Right Heart Catheterization & Acute Vasodilator Protocol

1. Insert a pulmonary artery floating catheter
2. Do hemodynamics readings on room air, which include: RAP, mPAP, PVR, COP/CI (use refrigerated saline), PAWP*, SaO_2, SvO_2, Systemic BP
3. If the patient is hypoxic (SaO_2 < 90% on room air) repeat the same hemodynamics on O_2
4. If PAWP is < 15 and diastolic dysfunction is clinically suspected, give 500 cc of normal saline, and repeat PAWP.
5. If the patient has IPAH (or CHD, CTEPH), then proceed to the next step:

↓

Start Nitric Oxide (NO) inhalation as per protocol at 20-40 ppm over 5 min
Or
Inhaled Iloprost, 5 mcg over 5-10 min

↓

Repeat hemodynamics as above

↓ **Positive** | ↓ **No response** | ↓ **Negative**

Definition of positive response:	**Definition of negative or no response:**
1. Reduction of mean PAP by >10 mmHg to reach an absolute value of mean PAP < 40 mmHg **AND** 2. Increase or no change in COP	No changes in hemodynamics, or **ANY** of the followings: 1. Decrease in systemic BP 2. Decrease in SaO_2 3. Decrease in COP

*** PAWP measurement:**

- PAWP should be correctly zeroed and referenced. The referencing (or leveling) is achieved by placing the air-fluid interface of the transducer at the intersection of a frontal plane passing midway between the anterior and posterior surface of the chest and a transverse plane lying at the junction of the 4th intercostal space and the sternal margin.
- PAWP should be measured at end-expiration
- If PAWP cannot be correctly measured, LVEDP should be obtained

Appendix 2: SAPH 6 MWT protocol

6 MINUTES WALKING TEST (6MWT PROTOCOL)	
Name:	Date:
MRN:	Time:
Age:	Diagnosis:
Sex:	Attending:
Height:	Technician:
Weight:	Medication:
Nationality:	
Smoker:	FIO_2:

6MWT Measurement		Baseline	End of test
	Time (min)		
	BP (mm/hg)		
	O_2 Sat %		
	HR (BPM)		
	Borg scale		

Patient stop the test:	
Reason to stop the test:	
Action taken:	
Symptoms at the end of test:	

6MWT Measurement		Date	Date	Date
Distance (m)				

Technician comments:	

Appendix 3: Criteria for Specialized Pulmonary Hypertension Center

Pulmonary Hypertension Specialized Center
Center of Excellence

PAH is a rare disease with progressive deterioration and complex management strategy. PAH patients should be managed at highly specialize center with multidisciplinary services and experience staff.

The aim of such centers is to undertake full assessment, initial investigation, and specific management of PAH patients by applying evidence-based diagnostic algorithm and offering PAH-target therapy by expert team in order to obtain best outcome.

PAH center should have a high volume of patients on chronic PAH therapy and accepting newly referred patients.

The following criteria are suggested for pulmonary hypertension specialized center, modified to comply with Saudi health system facilities:

Staff

- At least 2 PH consultant physicians specialists (usually from pulmonary and cardiology services)
- Cardiologist with extensive experience in RHC study and hemodynamic studies
- Intensivist with special interest in PH ventilated patients
- At least 1 registered nurse specialized in PH
- Radiologist with adequate experience in PH imaging
- Cardiologist with adequate experience in PH related echocardiography
- Psychologist
- Access to social workers

Volume of activity

- At least 50 patients with PAH or CTEPH in active follow-up
- At least 2 new patients with PAH or CTEPH per month, followed up for 3 years or more
- At least 20 vasoreactivity tests in PAH per year

Experience and quality of care

- Experience with all specific drugs
- Regular clinical review sessions
- Standardized operating procedures for diagnosis and treatment
- Assess indicators of outcome (survival)

Facilities and resources needed	• Specialized respiratory and cardiology department • Fully equipped ICU • Advanced echocardiography department • Cardiac hemodynamics • Pulmonary function laboratory • Cardiopulmonary stress testing • Sleep laboratory • CT and spiral-CT angiography • Nuclear medicine
Facilities	• Specialized outpatient department • Cardiac catheterization with vasoreactivity testing • Access to all drugs specific to PAH • 24-h on-call coverage
Information system	Database designed for the assessment of actions taken and results
Research activity	Referral centers should participate in collaborative clinical research in PAH, which includes phase II and phase III clinical trials
Other collaborative services:	• Rheumatology specialized cervices • Heart surgery and thoracic surgery (expertise in Pulmonary endarterectomy) • Lung and heart-lung transplantation • Congenital heart disease specialty services • Liver transplantation/liver hemodynamics • Invasive radiology services/pulmonary angiography • Infectious disease services (HIV unit, schistosoma)

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SAUDI GUIDELINES ON THE
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