Saudi guidelines on the diagnosis and treatment of pulmonary hypertension: 2014 updates

Main Guidelines

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Abstract:

The Saudi Association for Pulmonary Hypertension (previously called Saudi Advisory Group 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.

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 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.

Key words:

Pulmonary hypertension, pulmonary vascular resistance, modified functional class, target therapy, SAPH guidelines

The Saudi Association for Pulmonary Hypertension (previously called Saudi Advisory Group for Pulmonary Hypertension) has published the first Saudi guidelines on diagnosis and treatment of pulmonary arterial hypertension (PAH) back in 2008.[1] That guideline was very detailed and extensive and reviewed most aspects of pulmonary hypertension (PH).

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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 task force 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 PH, such as connective tissue disease associated with pulmonary arterial hypertension (CTD-APAH), hemolytic anemia associated with PH, portopulmonary arterial hypertension, congenital heart diseases (CHD)-APAH, chronic thromboembolic pulmonary hypertension (CTEPH), and creating detailed review articles. The second part will also include topics concerning updates on right ventricular (RV) 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 internal and 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 toward 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 of recommendation	Description
Class I	Good evidence/recommendation that a given treatment is effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	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	Description
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 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.

Pulmonary hypertension 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 <20 mmHg, the significance of mPAP value between 21 and 24 mmHg is unclear at this stage, but may necessitate close follow-up, especially in high-risk groups, such as systemic sclerosis (SSc) 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 PAH as follows: Patients with PAH have precapillary PH 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.[4,6-12] 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,[11] the US registry reported a much higher female preponderance of 3.9.[9] Such female predominance has been found to be less obvious in elderly patients.[13] 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%.[14]

Clinical Classification

As per the 5th PH World Congress, PH continues to be classified into five groups according to pathological, pathobiological, and therapeutic characteristics [Table 3].[15] It is very important to

Table 3: Updated clinical classification of PH (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
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 disorder 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)

categorize the patients within the right group, as approaches to therapy and management strategy vary significantly between different groups.

Hemodynamically, PH is classified into two groups; precapillary and postcapillary [Table 4]. Precapillary PH presents in the clinical Group I, III, IV, and V, while postcapillary (also called venous PH) presents in the clinical Group II.

Clinical pearls

- Transpulmonary pressure gradient (TPG) ≤12 mmHg indicates that PH is postcapillary (pulmonary venous hypertension) and is caused by elevated left atrial pressure (LAP). 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 postcapillary 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 trans-pulmonary gradient (TPG) is more accurate and physiological, as TPG might be influenced and affected by CO.[16] Value <7 indicates postcapillary pulmonary hypertension (PH), while value ≥7 indicates combined pre- and post-capillary component.

WHO Clinical Groups of Pulmonary Hypertension

Group I pulmonary arterial hypertension

It is well-recognizable that pulmonary arterial hypertension (PAH) has a complex multifactorial pathobiology that involves both biochemical pathways and cell types.[17,18] The increase in pulmonary vascular resistance (PVR) is related to vasoconstriction[19] and uninhibited proliferation of different cells presumably resulting from impaired apoptosis,[20] 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.[16] Endothelial dysfunction leads to impaired production of vasodilators and antiproliferative agents, such as nitric oxide and prostacyclin,

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 Postcapillary PH: TPG ≤12 mmHg or DPG <7 mmHg Combined post and precapillary PH: TPG >12 mmHg or DPG ≥7 mmHg	II

TPG (Trans-pulmonary gradient) = mPAP – PAWP; DPG (Diastolic pulmonary gradient) = dPAP – PAWP; PH = Pulmonary hypertension, TPG = Trans-pulmonary pressure gradient, DPG = Diastolic pulmonary gradient, mPAP = Mean pulmonary arterial pressure, dPAP = Diastolic pulmonary arterial pressure, PAWP = Pulmonary artery wedge pressure, LVEDP = Left ventricular end diastolic pressure

along with overexpression of many vasoconstrictors and mitogenic substances such as thromboxane A2, endothelin-1, and growth factors.[19,21]

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

Group II pulmonary hypertension due to left heart disease

The mechanism of PH in Group II patients is related to the passive backflow transmission of the high pulmonary venous pressure secondary to elevated LAP and/or left ventricular end diastolic pressure (LVEDP). In these cases, the TPG and/or the DPG are within the normal range [Table 4].

Detailed discussion of Group II diseases is presented later in this issue of the journal as a separate topic.

Group III pulmonary hypertension due to lung diseases and/or hypoxemia

The pathobiological mechanisms involved in Group III diseases are many and include hypoxic vasoconstriction, inflammation, mechanical stress related to hyper-inflated lungs, and loss of capillaries.[22,23] Direct toxic effect of inspired toxin such as cigarette smoke has also been suggested.

Detailed discussion of Group III diseases is presented later in this issue of the journal as a separate topic.

Group IV chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension may complicate acute pulmonary embolism in 1-5% of cases.[24] Nonresolution 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, neurohormonal mediators release causing bilateral vasoconstriction, inflammation, platelets dysfunction, and other pro-coagulant abnormalities.[25,26] 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.[27]

Detailed discussion of Group IV diseases is presented later in this issue as a separate topic.

Group IV pulmonary hypertension with unclear and/or multifactorial mechanisms

The pathobiology in this group is multifactorial.

Clinical Approach to Pulmonary Hypertension

Pulmonary hypertension 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 Registry to Evaluate Early and Long-Term PAH Disease Management REVEAL registry, 21% of patients had symptoms for >2 years before diagnosis.[6,28] Furthermore, in the French registry,[6] 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,[29] 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.

Due to the substantial evidence that early detection of the disease improves the outcome,[30] annual screening for selected high-risk patients is recommended. Such risk includes patients with SSc[31] 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 PAH in SSc) study has evaluated a two-step screening approach in patients with SSc with diffusion capacity (DLco) <60% and disease duration of >3 years.[32] The first step used a simple screening test, including the presence of telangiectasia, anticentromere antibodies, right-axis deviation on electrocardiogram, and low (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,[33] 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 RV systolic pressure 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.

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

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

Table 5: Definition of modified NYHA functional class

Modified New York Heart Association Functional Class	Definition
Functional Class I	Patients with PH in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or presyncope
Functional Class II	Patients with PH 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 presyncope
Functional Class III	Patients with PH 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 presyncope
Functional Class IV	Patients with PH 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

PH = Pulmonary hypertension, NYHA = New York heart association

Table 6: Echocardiographic criteria for the initial screening of high-risk patients for PH

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	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
	Criteria B TRV 2.9-3.4 m/s (or) sPAP 36-45 mmHg	C	
PH likely	TRV >3.4 m/s (or) sPAP >45 mmHg	B	Proceed to RHC

PH = Pulmonary hypertension, TRV = Tricuspid regurgitation jet velocity, sPAP = Systolic pulmonary artery pressure, RHC = Right heart catheterization, PAH = Pulmonary arterial hypertension

Initial diagnostic workup

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.

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.[34] 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 tricuspid regurgitation (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).

Right heart catheterization

Right heart catheterization 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.[4] 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 (MvO_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 to 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- 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 LVEDP should be directly measured[35] (class of recommendation: l). Appendix 1 illustrates Saudi Association for Pulmonary Hypertension (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.

The risks associated with RHC in patients with PH were evaluated in a multicenter, 5-year retrospective and 6-month prospective study.[36] A total of 7218 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.

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)
MvO_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 PAH-CHD and CTEPH
		Class of recommendation IIb in other forms of PH

RAP = Right atrial pressure, RHC = Right heart catheterization, CI = Cardiac index, CO = Cardiac output, MvO_2 = Mixed venous oxygen saturation, PVR = Pulmonary vascular resistance, mPAP = Mean pulmonary artery pressure, PAWP = Pulmonary arterial wedge pressure, PAH = Pulmonary arterial hypertension, LVEDP = Left ventricular end diastolic pressure, IPAH = Idiopathic pulmonary arterial hypertension, CHD = Congenital heart disease, CTEPH = Chronic thromboembolic pulmonary hypertension, PH = Pulmonary hypertension

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 three 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).[35]

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 III. However, 20% of PAH patients may have a mild restrictive defect.[37] DLco might also be reduced secondary to diminished pulmonary vascular volume and subsequent V/Q mismatch.[38] 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.[39-41]

Ventilation and perfusion (V/Q) lung scan: Class of recommendation to exclude chronic thromboembolic pulmonary hypertension: 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.[37] 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.[42] The sensitivity of V/Q scanning ranges from 90% to 100% with specificity of 94-100%.[43,44]

Computed tomography (CT) scan of the lung: Class of recommendation to exclude chronic thromboembolic pulmonary hypertension: 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.[45]

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.[46]

Finally, CT may also be useful in determining the extent of small-vessel involvement and the likelihood of improvement after thromboendarterectomy.[47] 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 chronic thromboembolic pulmonary hypertension: 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.[48] 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.[49] 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

Magnetic resonance imaging is a very promising tool for the evaluation of pathological changes in both the heart and the pulmonary circulation in PH patients.[50] 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.[51]

Other investigations: Class of recommendation: I

Testing for CTDs, hemoglobinopathy, HIV and schistosoma serology, thyroid function, hepatic ultrasound and viral hepatic screen, and liver and renal function tests:

Figure 1 illustrates the diagnostic algorithm in PH.

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.[52] However, the significance of these prognostic variables is less clear when applied to other conditions such as PAH associated with CTD, CHD, HIV infection or portal hypertension.

Demographics

Prognostic significance of demographic variables such as age and gender are inconsistent. In a retrospective study,[53] 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.[54] 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 a 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 New York Heart Association functional status

Baseline modified NYHA functional classification (FC) has a definite prognostic predictive value in patients with IPAH.[4] This predictive value is consistent even when NYHA classification is assessed either before or 3 months after the initiation of epoprostenol treatment.[55,56] Such FC should be always considered in managing patients with PH. Patients presented with the right heart failure before the initiation of treatment have a worse prognosis.[56]

Exercise tolerance

Objective assessment of exercise tolerance in patients with PAH is an important tool for evaluating disease severity,[56-58] disease outcome, and treatment effectiveness.[52,59] Six-min walk test (6-MWT) 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-min walk test 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 min walk.[60] 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

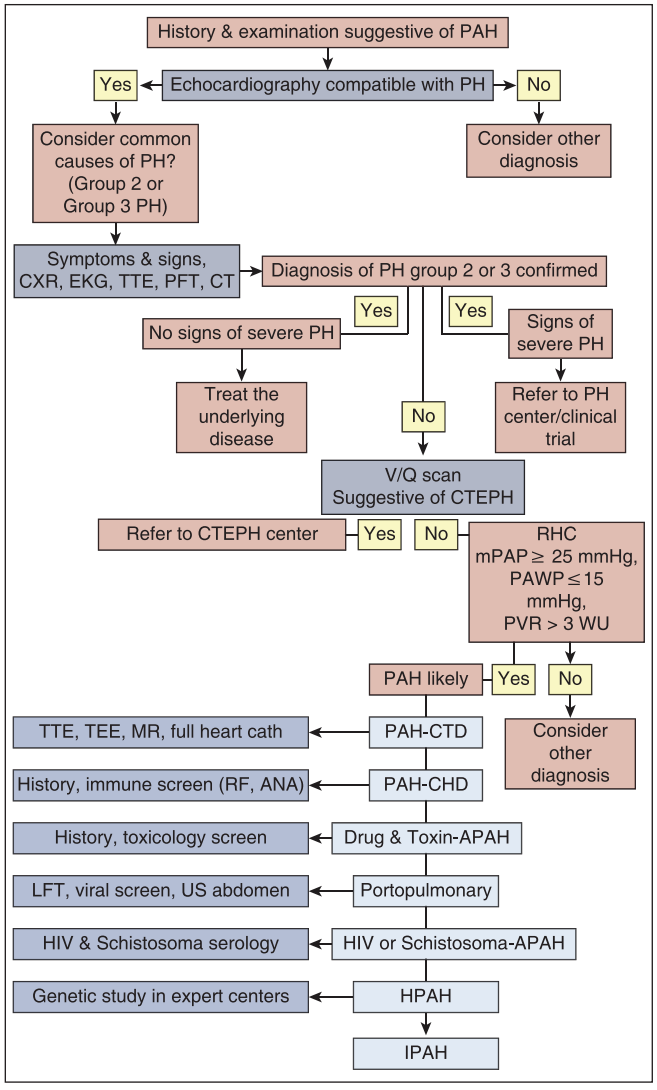

Figure 1: Evidence-based diagnostic algorithm of pulmonary hypertension

that although the absolute 6-MWT distance (i.e., >380-440 m) has prognostic implications, a change in 6-MWT distance with therapy dose not necessary impact the prognosis.[57]

Appendix 3 shows the SAPH 6-MWT protocol.

Cardiopulmonary exercise test is a more complicated test compared to 6-MWT. 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.[61] VO_{2max} determined by CPET has been found to be an independent predictor of survival in patients with IPAH.[58]

Patients with peak VO_{2max} of >10.4 ml/kg/min have a better survival than those with lower VO_{2max} (91% vs. 50%; $P < 0.0001$).[58] 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 a 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 (hazard ratio [HR], 3.89) and RA area index (HR, 1.54).[34,62,63] RV index (Tei index) is also found a predictive variable, but it could be affected by loading conditions and degree of TR.[64,65] 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.[66,67]

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 with posttreatment measurements in IPAH patients.[68]

Acute vasodilator testing

Acute vasodilator testing should be done in selected individuals using short acting pulmonary vasodilators.[69-72] 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 is strongly prohibited (class of recommendation for empiric use of CCBs in PAH patients: III).[73]

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 CO.[74,75] The incidence of the positive response in IPAH patients, who may be long-term responders to CCBs, is around 7-10%.[76]

Idiopathic pulmonary arterial hypertension patients, who are positive acute responders, have a very favorable prognosis and good response to CCBs.[15,77] 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 PAH-CHD and CTEPH patients showing positive acute response treated with modern targeted PH therapy (not CCBs).[78,79] 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 II, III, IV, and V is questionable.

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 RV dysfunction and mortality in PAH patients.[80] 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 MvO_2.[81]

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 a poorer outcome compared with 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).

Table 8: Suggested agents used for acute pulmonary vasoreactivity tests

Drugs	Route	Half-life	Dose range*	Initial dose	Increments^	Duration¥
Nitric oxide	Inhaled	15-30 s	–	20-40 ppm	–	5 min
Adenosine**	IV	5-10 s	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, ¥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, IV = Intravenous

- Low VO_{2max} (<10.4 ml/kg/min) and 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 cardiac index/CO (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 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 PH" in this issue of the Journal for a 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 predetermined goals are considered as the treatment target.[82]

Serial evaluation of disease progression/control should be done on a regular basis, usually 3-6 months intervals. Each evaluation should depend on a composite of data derived from clinical evaluation, exercise tests, biochemical markers, echocardiography, and hemodynamic assessments.[56,83,84]

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.[85]

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

Table 9: Parameters of goal-oriented strategy

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

RV = Right ventricular, TAPSE = Tricuspid annular plane systolic excursion, VO_{2max} = Peak oxygen consumption, SBP = Systolic blood pressure, RAP = Right atrial pressure, CI = Confidence interval, RHC = Right heart catheterization, BNP = Brain natriuretic peptide, NT = N terminal, CPET = Cardiopulmonary exercise test, NYHA = New York Heart Association, 6-MWT = Six-min walk test

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	

FC = Functional classification, PAH = Pulmonary arterial hypertension, IPAH = Idiopathic pulmonary arterial hypertension, HF = Heart failure

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	
Calcium channels blockers			✓	I	I	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. and 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	

ERA = Endothelin receptors antagonist, NO = Nitric Oxide, PD-5 Inh.= Phosphodiesterase-5 inhibitors, sGC = Soluble guanylate cyclase, TK = Tyrosine kinase, PAH = Pulmonary arterial hypertension, FC = Functional class, IV = Intravenous, CTEPH = Chronic thromboembolic pulmonary hypertension

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, and 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 New York Heart Association functional class II patients

Recent studies showed that early intervention of PAH patients with very minimal symptoms and good exercise tolerance is appropriate and beneficial.[86]

Modified NYHA FC II patients should be:

- Enrolled in a rehabilitation program.[87,88] (class of recommendation: I).
- Treated with general supportive measures and with initiation of background therapy that includes oral anticoagulants[77,89] (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 CCBs.[15,77] (class of recommendation: I). Maintenance of the response (controlled/good prognosis) should be confirmed after 3-6 months of treatment as well as long-term, as some patients may convert from vasoreactive to non-vasoreactive over time.[78,90] However, it should be emphasized that CCBs are contraindicated in patients with right-sided heart failure, even if they are vasoreactive [Table 11].
- Nonvasoreactive patients should be treated by specific target therapy, including bosentan,[91] ambrisentan,[92] sildenafil,[93] and tadalafil[94] (level of evidence: A). Beraprost sodium[95] has also been used and approved in Japan and many Asian countries (level of evidence: B). Newer drugs, macitentan[96] and riociguat,[97] may also be approved for FC II patients based on recently completed studies.

Modified New York Heart Association functional class 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).

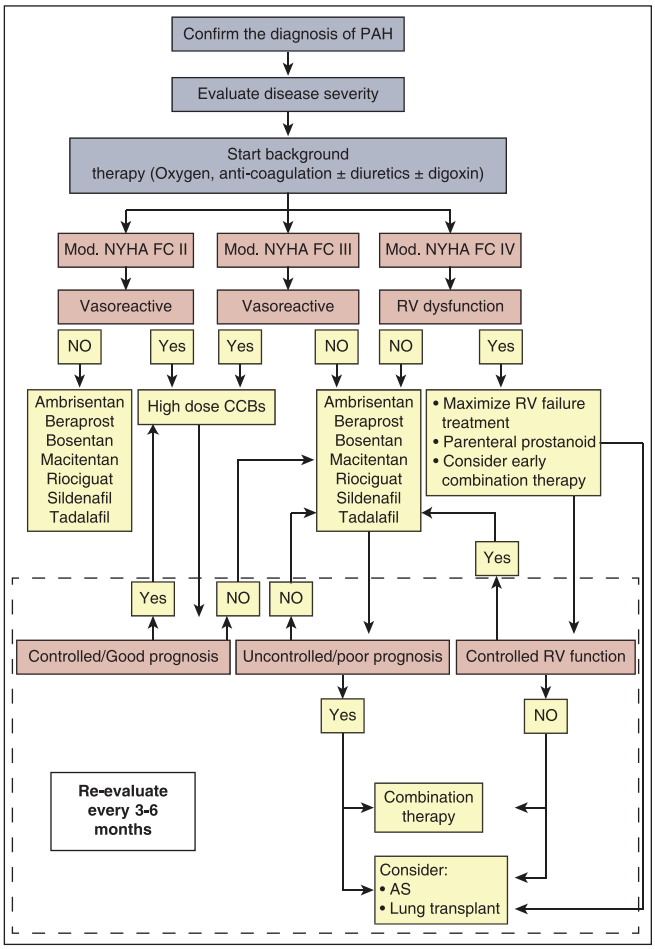

Figure 2: Pulmonary arterial hypertension, evidence-based treatment algorithm

- 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 3-6 months of treatment. Long-term stability on CCBs therapy should always be monitored.
- Nonvasoreactive (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 4 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. Ambrisentan 5 mg OD (level of evidence A), or
v. 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 two 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 PAH in this issue of the journal for a detailed discussion for each class of therapy):
   i. Sildenafil plus inhaled iloprost[98]
   ii. Inhaled iloprost plus bosentan[99]
   iii. Sildenafil plus bosentan[100]
   iv. Tadalafil plus bosentan[101]
   v. Prostanoid plus sildenafil[102]
   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 intravenous (IV) epoprostenol infusion.[103] (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[104] (class of recommendation: I) or IV[105] (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.[106] (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.[107] (class of recommendation: IIb).
   v. In selected individuals, refer the patient for lung transplantation assessment.[108] (class of recommendation: I).

Modified New York Heart Association functional class 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 RV 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 RV function should be treated exactly as modified NYHA FC III, nonvasoreactive, 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.[109,110] (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 especially those with recurrent syncope and/or right sided heart failure. These procedures should be performed only in experienced centers.

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