Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: General management for pulmonary hypertension

Majdy M. Idrees, John Swiston[1], Robert D. Levy[1]

Division of Pulmonary Medicine, Prince Sultan Medical Military City, Riyadh, Saudi Arabia, [1]Vancouver General Hospital, Vancouver, BC, Canada

Address for correspondence:
Dr. Majdy M Idrees, MD, FCCP, Pulmonary Medicine, Prince Sultan Medical Military City, P. O. Box 7897 (C 110), Riyadh 11159, Saudi Arabia.
E-mail: majidrees@gmail.com

Submission: 29-03-2014
Accepted: 05-04-2014

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.134041

Abstract:

Treatment of pulmonary hypertension (PH) patients is challenging and should only be initiated after a comprehensive diagnostic evaluation. Such treatment should ideally be done in specialized centers with full capability for hemodynamic measurements, having access to a broad range of PAH therapies, and adequate experience in the management of critically ill patients.

The following discussion is intended to review the general measures and the non-specific (supportive) therapy used in managing PH patients, while the specific therapy will be discussed in a subsequent different article.

Key words:

Pulmonary hypertension, general measures, supportive therapy, Saudi association for pulmonary hypertension guidelines

In the past decade, management of pulmonary arterial hypertension (PAH) has undergone a major evolution. Modern therapy has led to a significant improvement in patients' symptomatic status and quality of life, and also led to a slower rate of clinical deterioration.[1] A meta-analysis performed on 23 randomized controlled trials in PAH patients has reported a 43% reduction in mortality and a 61% reduction in hospitalizations in patients treated by modern drug therapies for an average of 14.4 weeks compared with placebo.[2]

Treatment of pulmonary hypertension (PH) patients is challenging. Such treatment should ideally be carried out in specialized centers with full capability for hemodynamic measurements, having access to a broad range of PAH therapies, and adequate experience in the management of critically ill-patients.

The following discussion is intended to review the general measures and the nonspecific (supportive) therapy used in managing PH patients, whereas the specific therapy will be discussed in a subsequent different article.

General Measures

Physical activity and rehabilitation: (Level of evidence: A; class of recommendation: I)

A balanced approach to physical activities to maintain conditioning and muscular strength is helpful and should be encouraged whenever possible. Care should be focused in order to not aggravate the symptoms or compromise safety. Clearly, a high intensity of activities leading to severe dyspnea, syncope, or chest pain should be avoided. Appropriate adjustments of daily activities may improve the quality of life and well-being, and can reduce the frequency and intensity of symptoms. A number of recent studies have confirmed the value of a training and rehabilitation program in improving exercise performance and quality of life.[3-6]

Travel/high altitude: (Level of evidence: C; class of recommendation: IIa)

Although, there are no direct studies addressing the need for supplemental oxygen during a prolonged flight, the known pathophysiological effect of hypoxia on the pulmonary circulation and the resultant pulmonary vasoconstriction in PAH patients suggests the need for inflight oxygen administration. Oxygen supplementation in PAH patients should be offered to all patients in modified New York Heart Association (NYHA) functional Class III and IV, and to those with arterial oxygen saturation <90% at sea level. Simulated hypoxic challenge utilizing a hypoxic inspired gas mixture (15% FiO_2) in the lab can be helpful in determining the need of supplement oxygen at high altitude in those patients with resting room air oxygen saturation between 92 and 95%.[7] Similarly, patients going to high altitudes (above 1500-2000 m) should be instructed to use supplemental oxygen.

Pregnancy and birth control: (Level of evidence: C; class of recommendation: I)
The hazard of pregnancy in PH is discussed in detail in a separate review elsewhere in this issue of the journal. Nevertheless, it suffices to mention here that the potential risk for pregnancy is probably largely related to pregnancy-induced increased cardiac output and hyper-dynamic circulation,[8] which will be poorly tolerated by the already stressed right ventricular (RV) in patients with PH, and is associated with an increased rate of morbidity and mortality for mother and baby as high as 50% in severe cases.[9-11] Despite the fact that successful pregnancies have been reported in idiopathic pulmonary arterial hypertension (IPAH) patients,[12] it is strongly agreed between all experts in the field of pulmonary vascular diseases and clinical guidelines that pregnancy is to be avoided or terminated in women with advanced PH.

Prevention of infections: (Level of evidence: C; class of recommendation: I)
All conditions that cause increase work of breathing, hypoxemia, and reduction in blood oxygen carrying capacity are poorly tolerated by PAH patients. A prospective survey has found that patients with PAH are susceptible to developing pneumonia, which is the cause of death in 7% of cases.[13] Despite the lack of direct evidence, vaccination against influenza and pneumococcal pneumonia is recommended. Persistent fever in patients with intravenous (IV) catheter for continuous administration of epoprostenol should always raise the suspicion of catheter-related infection and should be dealt with promptly.

Anemia and polycythemia: (Level of evidence: C; class of recommendation: IIa)
Patients with PH are highly sensitive to anemia resulting in reduction of the blood oxygen carrying capacity since this cannot be compensated for in view of limited capacity to increase cardiac output in this group of patients. This will eventually lead to a drop in oxygen delivery and worsening of the symptoms and hemodynamics. Subsequently, mild anemia should be aggressively treated, and probably prevented in PH patients with high risk, such as young menstruating women. Furthermore, recent evidence has suggested that the red blood cells obtained from patients with PH are defective and fail to release adenoside-tri-phosphate (ATP) (a known agonist for enhanced nitric oxide [NO] synthesis), and might contribute to the increased pulmonary vascular resistance (PVR) in PH patients.[14]

Finally, although polycythemia secondary to long-standing hypoxia might increase blood viscosity that can interfere with proper oxygen delivery and might worsen symptoms, it should be emphasized that phlebotomy is indicated only if hematocrit is above 65% in symptomatic patients (headache, poor concentration).[15] Overuse of phlebotomy can be hazardous,[16] but unfortunately continues to be practiced by many treating physicians.

Elective surgery: (Level of evidence: C; class of recommendation: IIa)
The complexity of perioperative management in PH is discussed in detail by a separate review in this issue of the journal. Recent evidence has suggested that PH is a risk factor for worse outcomes in both cardiac and noncardiac surgeries.[17-19] This risk is believed to be increased with the severity of modified NYHA functional classes and disease severity. The type of anesthesia is left to the experience of the anesthetist, as no conclusive evidence is available to prefer one method of anesthesia over the others. However, regional anesthesia using a low epidural dose is probably the safest techniques in these patients since it minimizes the hemodynamic compromise associated with systemic afterload reduction. Spinal anesthesia, however, should be avoided in most cases as it may cause poorly tolerated hemodynamic changes at induction and during recovery. General anesthesia should also be carefully considered as it can increase PVR by sympathetic activation during airway intubation, positive pressure mechanical ventilation, or anesthetic agents that can affect RV afterload.[20,21]

The intra-operative use of an indwelling pulmonary artery floating catheter to continually monitor cardiopulmonary hemodynamics is recommended by some experts, but continue to be a controversial issue; however, there is no direct evidence to show that this approach improves the outcomes.[22]

Patients on IV epoprostenol treatment should continue on their treatment. In case a prolonged period of withdrawal is expected (>12-24 h), it is advisable to shift patients on inhaled or oral therapy to IV treatments and revert to the original therapy subsequently.

Alternatively, consideration should be given to using inhaled NO and/or inhaled Iloprost intra- or post-operatively on an elective basis to prevent or minimize the risk of acute PH crisis. Finally, anticoagulant treatment should be interrupted for the shortest possible time and deep venous thrombosis prophylaxis should be strongly considered.

Psychological assistance: (Level of evidence: C; class of recommendation: IIa)
Patients with PH are usually young, and exercise limitation may interfere considerably with their previous lifestyle. Depression is quite common in this group of patients and should be carefully evaluated and treated. Early referral to a psychiatrist or psychologist should be considered. Some anti-depressant agents may have complex drug interactions with PAH specific therapies and special care should be given for this aspect. The role of PH multidisciplinary team is important in supporting patients with adequate information.[23]

Table 1 summarized the recommendations for the general measures in managing PH patients.

Supportive Therapy

Oxygen: (Level of evidence: C; class of recommendation: I)
The pathophysiological mechanisms for hypoxemia in PAH are multifactorial, and include low mixed venous oxygen saturation caused by low cardiac output, increased oxygen extraction and to a lesser extent, altered ventilation perfusion matching. In patients with congenital heart disease associated with PAH and Eisenmenger syndrome, hypoxemia is related to the presence of right-to-left shunting and is refractory to increased inspired oxygen.

Table 1: Recommendations for general measures in PH

Recommendation	Level of evidence	Class of recommendation
Rehabilitation and appropriate physical conditioning should be offered to PH patients	A	I
Offering in-flight oxygen to all NYHA FC III and IV patients, and those with resting saturation <90%	C	IIa
Pregnancy to be avoided or terminated early in all PH patients	C	I
Influenza and pneumococcal vaccine to be offered to all PH patients	C	I
Anemia to be treated in all PH patients	C	IIa
Routine/elective transfusion of blood products	C	III
Repeated phlebotomy to treat non-symptomatic polycythemia	C	III
Epidural anesthesia should be used, whenever possible	C	IIa
General anesthesia can be used with extreme caution	C	IIb
Spinal anesthesia in PH patients	C	III
Psychological support to be offered to all PH patients	C	IIa
PAH patients should be referred to expert centers	C	I

PH = Pulmonary hypertension, NYHA = New york heart association, FC = Functional class

Oxygen administration has been demonstrated to reduce the PVR in patients with PAH, but there are no randomized studies to suggest that long-term oxygen therapy is beneficial in PH patients. Despite the lack of such evidence, extrapolation of such data from chronic obstructive pulmonary disease (COPD) literatures suggests that it is generally important to maintain oxygen saturation >90% to avoid hypoxia-induced pulmonary vasoconstriction,[24] which can be detrimental in PH. A retrospective analysis from the Mayo clinic experience has suggested that systemic arterial oxygen saturation is a predictive of survival in patient with IPAH.[25] Another review reported that the low values of systemic arterial oxygen saturation in patients with IPAH were associated with a high incidence of sudden death.[26]

The use of high flow oxygen treatment in patients with PAH associated with cardiac shunts is more controversial. Indeed, the risk of oxygen toxicity should be weighed against any small benefit that can be accomplished by this therapy is this particular situation. In a controlled study on Eisenmenger syndrome patients, nocturnal oxygen therapy was found to have no significant effect on hematological variables, quality of life, or survival.[27]

Oral anticoagulant treatment: For idiopathic pulmonary arterial hypertension, heritable PAH (HPAH) and anorexigenic drugs-pulmonary arterial hypertension (PAH): (Level of evidence: C; class of recommendation: IIa) for other PAH: (Level of evidence: C; class of recommendation: IIb)

The rationale for the use of anticoagulant treatment in PAH patients is based on the presence of traditional risk factors for venous thromboembolism, such as heart failure and sedentary lifestyle, and the demonstration of *in situ* thrombotic activities and of similar changes in the pulmonary microcirculation.[28-31] Such processes may further compromise the cross-sectional area of the pulmonary vasculature, leading to a progressive increase in PVR and contributing to the deteriorating course seen in PAH patients. Favorable effects and improved survival have been reported with oral anticoagulation in patients with IPAH, HPAH, and anorexigenic drugs-related PAH.[32,33]

It should be recognized, however, that only limited data are available evaluating the role of anticoagulation therapy in PAH patients who are on modern PAH-specific therapy. In a systematic review of seven observational studies that evaluated the effect of anticoagulation in PAH patients, five studies found a mortality benefit.[34]

The target International Normalized Ratio in patients with IPAH is 1.5-2.5. The risk of bleeding should always be weighed against the benefit of such treatment, especially in certain situations, such as portopulmonary hypertension with esophageal varices or Eisenmenger syndrome presenting with hemoptysis. Finally, it is a common practice to anticoagulate PAH patients receiving therapy with long-term IV prostacyclin due in part to the additional risk of catheter-associated thrombosis.

Fluid management and diuretics: (Level of evidence: C and class of recommendation: I)

Despite the lack of strong scientific evidence, clinical experience has clearly shown that diuretics have an important role in treating the symptomatic manifestations of right-sided heart failure in PAH patients. They appear to provide symptomatic relief by reducing pulmonary capillary congestion and improving the geometry and function of the right ventricle and interventricular septum.

Maintaining near-normal intravascular volume with diuretics, and careful dietary salt and fluid restriction, is generally recommended for the long-term management of PAH patients. However, rapid and excessive diuresis may lead to systemic hypotension, renal insufficiency, and syncope. Serum electrolytes and indices of renal function should be followed closely in patients receiving diuretic therapy. The choice of the diuretics is left to the treating PAH expert, but the addition of aldosterone antagonists should generally be considered.

Digitalis and dobutamine: (Level of evidence: C and class of recommendation: IIb)

Inotropic agents have been considered for the treatment of PH patients with low RV cardiac output. Short-term IV administration of digoxin in IPAH has shown to produce a modest increase in cardiac output and a significant reduction in circulating norepinephrine levels.[35] Digoxin has also shown to improves the RV ejection fraction of patients with WHO Group III PH due to COPD and biventricular failure.[36] On the contrary, digitalis was found to directly increase PVR and

Table 2: Recommendation for supportive therapy in PH patients

Recommendation	Level of evidence	Class of recommendation
Long-term oxygen therapy is indicated to PH patients when resting PaO_2 is ≤60 mmHg	C	I
Oral anticoagulation therapy to be considered in IPAH, HPAH, and drug-related PAH	C	IIa
After considering the risk versus the benefit, oral anticoagulation therapy to be considered in other forms of PAH	C	IIb
Salt and water restriction and diuretic therapy is indicated in PH patients with signs of RV failure or fluid over-load	C	I
Digoxin in PH patients with signs of RV failure	C	IIb
Supraventricular arrhythmia is not uncommon in PH patients, and should be promptly diagnosed and treated	C	I

RV = Right ventricular, PH = Pulmonary hypertension, PAH = Pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, IPAH = Idiopathic pulmonary arterial hypertension

adversely affect exercise capacity in patients with chronic pulmonary diseases in the absence of clear RV failure.[37]

With the current state of knowledge and because of the lack of strong evidence, the use of digoxin in PAH patients with refractory right heart failure is based primarily on the judgment of the physician rather than on scientific evidence of efficacy and cannot be recommended at this stage.

In patients with end-stage PH, treatment with IV dobutamine is recommended by some experts, despite the lack of well-designed studies.[38] Similar to the effect in advanced left ventricular failure, this treatment often results in short-term clinical improvement and considered as a form of "palliative" treatment.

Treatment of arrhythmia in pulmonary hypertension: (Level of evidence: C; class of recommendation: I)

The annual incidence of supraventricular arrhythmias in patients with severe PAH is 2.8% and they have a negative impact on the prognosis.[39] Atrial flutter is the typical type of arrhythmia that complicates right atrial enlargement secondary to the pressure load from the right ventricle.

It is notable that patients with severe PAH poorly tolerate the loss of coordinated atrial contraction resulting in lowered cardiac output, and hence, the restoration of sinus rhythm is recommended, as it has been shown to contribute to an improvement in outcome.[40]

Digoxin, verapamil, or amiodarone might be considered as treatment options for supraventricular tachyarrhythmia in PH patients. However, such antiarrhythmic therapy might be limited by lack of efficacy and adverse effects, particularly the negative inotropy in the setting of RV dysfunction. In this respect, a potential approach with ablation might be considered in highly specialized centers.[41]

Table 2 summarizes the recommendations for supportive therapy in managing PH patients.

References

1. Idrees M. Pulmonary hypertension: Another light in the dark tunnel. Learning the lesson from cancer. Ann Thorac Med 2013;8:69-70.
2. Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394-403.
3. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, *et al*. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation 2006;114:1482-9.
4. Fox BD, Kassirer M, Weiss I, Raviv Y, Peled N, Shitrit D, *et al*. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. J Card Fail 2011;17:196-200.
5. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, *et al*. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2009;34:669-75.
6. Al Moamary MS, Alorainy H, Al-Hajjaj MS. Pulmonary rehabilitation: A regional perspective evidenced-based review. Ann Thorac Med 2014;9:3-7.
7. British Thoracic Society Standards of Care Committee. Managing passengers with respiratory disease planning air travel: British Thoracic Society recommendations. Thorax 2002;57:289-304.
8. Manes A, Galiè N, Branzi A. Women and pulmonary arterial hypertension. Eur Respir J 2003;8:219-27.
9. Nelson DM, Main E, Crafford W, Ahumada GG. Peripartum heart failure due to primary pulmonary hypertension. Obstet Gynecol 1983;62:58s-63.
10. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: A systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31:1650-7.
11. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J 2003;24:761-81.
12. Nootens M, Rich S. Successful management of labor and delivery in primary pulmonary hypertension. Am J Cardiol 1993;71:1124-5.
13. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, *et al*. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216-23.
14. Sprague RS, Stephenson AH, Ellsworth ML, Keller C, Lonigro AJ. Impaired release of ATP from red blood cells of humans with primary pulmonary hypertension. Exp Biol Med (Maywood) 2001;226:434-9.
15. Deanfield J, Thaulow E, Warnes C, Webb G, Kolbel F, Hoffman A, *et al*. Management of grown up congenital heart disease. Eur Heart J 2003;24:1035-84.
16. Rose SS, Shah AA, Hoover DR, Saidi P. Cyanotic congenital heart disease (CCHD) with symptomatic erythrocytosis. J Gen Intern Med 2007;22:1775-7.
17. Rodriguez RM, Pearl RG. Pulmonary hypertension and major surgery. Anesth Analg 1998;87:812-5.
18. Bonnin M, Mercier FJ, Sitbon O, Roger-Christoph S, Jaïs X, Humbert M, *et al*. Severe pulmonary hypertension during pregnancy: Mode of delivery and anesthetic management of 15 consecutive cases. Anesthesiology 2005;102:1133-7.
19. Kuralay E, Demírkiliç U, Oz BS, Cíngöz F, Tatar H. Primary pulmonary hypertension and coronary artery bypass surgery. J Card Surg 2002;17:79-80.
20. Price LC, Montani D, Jaïs X, Dick JR, Simonneau G, Sitbon O, *et al*. Noncardiothoracic nonobstetric surgery in mild-to-moderate pulmonary hypertension. Eur Respir J 2010;35:1294-302.

21. Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: Pathophysiology and anesthetic approach. Anesthesiology 2003;99:1415-32.
22. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, *et al*. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48:2546-52.
23. Girgis A, Sanson-Fisher RW. Breaking bad news: Consensus guidelines for medical practitioners. J Clin Oncol 1995;13:2449-56.
24. Khan JH, Lababidi HM, Al Moamary MS, Zeitouni MO, Al-Jahdali HH, Al Amoudi OS, *et al*. The Saudi guidelines for the diagnosis and management of COPD. Ann Thorac Med 2014;9:55-76.
25. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: Natural history and the importance of thrombosis. Circulation 1984;70:580-7.
26. Kanemoto N. Natural history of pulmonary hemodynamics in primary pulmonary hypertension. Am Heart J 1987;114:407-13.
27. Sandoval J, Aguirre JS, Pulido T, Martinez-Guerra ML, Santos E, Alvarado P, *et al*. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med 2001;164:1682-7.
28. Pietra GG, Edwards WD, Kay JM, Rich S, Kernis J, Schloo B, *et al*. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. Circulation 1989;80:1198-206.
29. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, *et al*. Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 2004;43:25S-32.
30. Friedman R, Mears JG, Barst RJ. Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 1997;96:2782-4.
31. Eisenberg PR, Lucore C, Kaufman L, Sobel BE, Jaffe AS, Rich S. Fibrinopeptide A levels indicative of pulmonary vascular thrombosis in patients with primary pulmonary hypertension. Circulation 1990;82:841-7.
32. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.
33. Frank H, Mlczoch J, Huber K, Schuster E, Gurtner HP, Kneussl M. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest 1997;112:714-21.
34. Johnson SR, Mehta S, Granton JT. Anticoagulation in pulmonary arterial hypertension: A qualitative systematic review. Eur Respir J 2006;28:999-1004.
35. Rich S, Seidlitz M, Dodin E, Osimani D, Judd D, Genthner D, *et al*. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 1998;114:787-92.
36. Mathur PN, Powles P, Pugsley SO, McEwan MP, Campbell EJ. Effect of digoxin on right ventricular function in severe chronic airflow obstruction. A controlled clinical trial. Ann Intern Med 1981;95:283-8.
37. Coates AL, Desmond K, Asher MI, Hortop J, Beaudry PH. The effect of digoxin on exercise capacity and exercising cardiac function in cystic fibrosis. Chest 1982;82:543-7.
38. Naeije R, Vachiéry JL. Medical therapy of pulmonary hypertension. Conventional therapies. Clin Chest Med 2001;22:517-27.
39. Tongers J, Schwerdtfeger B, Klein G, Kempf T, Schaefer A, Knapp JM, *et al*. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. Am Heart J 2007;153:127-32.
40. Ruiz-Cano MJ, Gonzalez-Mansilla A, Escribano P, Delgado J, Arribas F, Torres J, *et al*. Clinical implications of supraventricular arrhythmias in patients with severe pulmonary arterial hypertension. Int J Cardiol 2011;146:105-6.
41. Bradfield J, Shapiro S, Finch W, Tung R, Boyle NG, Buch E, *et al*. Catheter ablation of typical atrial flutter in severe pulmonary hypertension. J Cardiovasc Electrophysiol 2012;23:1185-90.

How to cite this article: Idrees MM, Swiston J, Levy RD. Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: General management for pulmonary hypertension. Ann Thorac Med 2014;9:S74-8.

Source of Support: Nil, **Conflict of Interest:** None declared.