International Journal of Medicine Research
ISSN: 2455-7404; Impact Factor: RJIF 5.42
www.medicinesjournal.com
Volume 1; Issue 2; May 2016; Page No. 07-12

Guidelines for management of pulmonary hypertension in specific patient situations

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Abstract
The options for pharmacotherapy in patients with PAH include several drug classes and delivery routes. The choice of therapy should be made by experienced clinicians and must be based upon an appropriately established diagnosis and evaluation of the patient's disease severity. Available evidence is sufficient to inform a limited number of strong guideline recommendation statements regarding the effect of a specific therapy or combination of therapies on select outcomes in distinct groups of patients defined according to disease severity. Where current evidence is insufficient to inform strong guideline recommendations, expert consensus may provide reasonable advice in evaluating available data and reasonable therapeutic choices. Well-designed studies are needed to compare approaches to therapy in specific groups of patients. As such information and new therapies become available, a reassessment of appropriate clinical advice for the pharmacologic therapy for adult patients with PAH will be required.

Keywords: Pulmonary hypertension, pharmacotherapy, Specific Patient Situations

1. Introduction

Pulmonary hypertension (PH) is an increase in mean pulmonary arterial pressure (PAP), which can be caused by or associated with a wide variety of conditions. Idiopathic pulmonary arterial hypertension (PAH) is a rare disorder that can be defined as a sustained elevation in PAP and pulmonary vascular resistance, with normal pulmonary artery wedge pressure, in the absence of a known cause. It is a diagnosis of exclusion after other possible causes of PH have been excluded. It is a severe and often rapidly progressive illness in many cases. The injury to the pulmonary endothelium causes a tendency to in situ thrombosis in the pulmonary arterial tree, the so-called thrombotic pulmonary arteriopathy. The disease process continues through vascular scarring, endothelial dysfunction and proliferation of smooth muscle cells within the intima and media of the pulmonary arterial tree, causing progressive pulmonary arterial hypertension. This leads to progressive right heart strain due to obliteration of small pulmonary arterial vessels, and eventually right heart failure.

2. Pulmonary Hypertension at a Glance.

2.1 Epidemiology

Idiopathic PAH is rare. However, the prevalence of PAH is higher in certain patient groups, such as those with systemic sclerosis, portal hypertension, congenital heart disease and HIV infection. The prevalence of PAH is estimated at 15-52 per million. The incidences are estimated to be 1-3.3 per million per year for idiopathic PAH and 1.75-3.7 per million per year for chronic thromboembolic PH.PH is more common in severe respiratory and cardiac disease, occurring in 18-50% of patients assessed for transplantation or lung volume reduction surgery, and in 7-83% of those with diastolic heart failure. Between 0.5% and 4% of patients develop chronic thromboembolic PH after acute pulmonary embolism. There is an increased risk for patients presenting with large, recurrent or unprovoked clots [1].

2.2 Presentation

Most commonly presents with progressive breathlessness, weakness and tiredness. Exertional dizziness and syncope may also develop. Oedema and ascites tend to occur late in the disease. Angina and tachyarrhythmias, particularly atrial flutter, may also occur. Haemoptysis is uncommon but may occur in Eisenmenger's syndrome and chronic thromboembolic PH. Clinical signs include right ventricular (parasternal) heave, a loud pulmonary second heart sound, murmur of pulmonary regurgitation, systolic murmur of tricuspid regurgitation, raised jugular venous pressure, peripheral Oedema and ascites. These signs may be subtle or absent in early disease. There may also be signs of associated conditions, such as connective tissue disease or liver disease [1].

2.3 Management

Specific treatments exist for PAH and chronic thromboembolic PH. In PAH due to left heart disease, lung disease or hypoxia, treatment is best directed at the underlying condition **[1]**. Patients are best managed through regional specialist units that have the expertise to manage their severe illness, relevant complex investigations, expensive medication and clinical trial administration.

1. Management of any underlying cause.
2. Although some drugs seem to have significant effects on symptoms and exercise tolerance in the short term, there is little useful information on their effect on long-term survival in this devastating illness, an issue that future trial designs will have to address [2].
3. Atrial septostomy is a palliative procedure that may provide some benefit to patients whose condition is deteriorating.

2.3.1 Cardio supportive therapy

Supplemental oxygen can help symptomatically with exercise tolerance. Diuretics are used to treat right heart failure and remove peripheral Oedema, along with digoxin as a positive inotrope. There are no convincing trial data to support their use but consensus is that they are helpful. High-dose calcium-channel blockade (e.g. diltiazem titrated to 480-720 mg/day or nifedipine titrated to 60-120 mg/day) may be used for idiopathic

PAH. Because of the potential negative inotropic effect, treatment should not be started without a positive acute vasoreactivity test [1].

2.3.2 Prostacyclin analogues

Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation. Various prostacyclin analogues may be used to treat the condition. Most need to be given by continuous intravenous infusion, usually through a long-term indwelling central venous catheter. A Cochrane review of intravenous prostacyclin analogues found evidence of short-term benefit (up to 12 weeks of treatment) in exercise capacity, NYHA functional class and cardiopulmonary Haemodynamics. There was also some evidence that patients with more severe disease showed a greater response to treatment [3].

2.3.3 Endothelin-A receptor antagonists

Endothelin is a potent vasoconstrictor of vascular smooth muscle. Bosentan, Ambrisentan have been shown to improve exercise capacity and time to clinical worsening. Bosentan may cause reversible abnormalities in LFTs so regular monitoring of LFTs is needed [1].

2.3.4 Phosphodiesterase-5 inhibitors

These drugs modulate the effects of nitric acid on vascular tone via their effect on cyclic GMP and appear to be relatively selective pulmonary arterial vasodilators. They are traditionally used to treat erectile dysfunction and sildenafil has been shown to have beneficial effects in primary PH, being licensed in the USA for its treatment [4].

2.3.5 Drugs under clinical investigation

Other drugs under current clinical investigation include serotonin antagonists, vasoactive intestinal peptide, stimulators of soluble Guanylate, Cyclase and tyrosine kinase inhibitors [5].

2.3.6 Transplantation

Single/double-lung or cardiopulmonary transplantation may be considered in some severe cases. With pulmonary protection and immunosuppression, the long-term prognosis after lung and heart-lung transplant is good [6].

3. Management of Pulmonary Hypertension in Specific Patient Situations

3.1 Pregnancy

Pregnancy was addressed in the 2004 ACCP Medical Therapy Guidelines document [7]. Following is an update to that section of the document. Many patients with PAH are women of childbearing age. The hemodynamic demands of pregnancy are substantial and include an increase of 30% to 50% in blood volume, a similar increase in CO, a 10- to 20-beat/min increase in heart rate, an increase in stroke volume, and decreases in both systemic vascular resistance and BP [7, 8]. These hemodynamic changes begin during the first trimester and peak at 20 to 24 weeks of gestation. During labor, there are further increases in CO, and the BP also increases with uterine contractions. Immediately postpartum there are marked volume shifts, with cardiac filling pressures increasing dramatically as a result of decompression of the vena cava and the return of uterine blood into the systemic circulation. The hemodynamic changes associated with pregnancy regress by approximately 6 weeks after delivery. The physiologic changes induced by pregnancy impose a marked hemodynamic stress in women with IPAH, leading to a previously estimated 30% to 50% mortality rate [9, 10]. More recent data indicate that the outcome of pregnancy in PAH has improved (a 12% maternal mortality rate was reported in a recent survey [11]. at least when PAH is well controlled. However, pregnancy remains associated with a substantial mortality risk. Because of potential maternal and fetal morbidity and mortality, most experts recommend effective contraception and consideration of early termination if pregnancy occurs in a patient with PAH [12, 13].

In addition to the hemodynamic stresses of pregnancy, hormonal changes during and immediately following pregnancy may also be detrimental from a pathophysiologic standpoint. Anecdotal experience suggests that even if a woman successfully delivers a term infant, her pulmonary hypertension may progress during pregnancy and remain worse after pregnancy. Furthermore, there appears to be an increased incidence of small-for-gestational-age infants born to women with IPAH [14], as well as an increased incidence of congenital anomalies. There are several reports of successful treatment of pregnant patients with IPAH with chronic IV epoprostenol [15, 18]. Inhaled nitric oxide [19, 21], and oral CCBs [11, 22].

In general, current management includes early hospitalization for closer monitoring once the fetus is viable, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and Dobutamine, as needed. In addition, the use of a pulmonary artery catheter for close hemodynamic monitoring may be helpful. Recommendations for the optimal mode of delivery remain controversial; early concerns of high mortality with cesarean section delivery led to an emphasis on vaginal delivery, and a series of seven women with severe pulmonary hypertension who were successfully delivered by the vaginal route has been described [23]. Successful treatment during cesarean section delivery has also been reported, which may partly be due to the changes in the selection and use of anesthetics [24].

In a meta-analysis of the outcome of pulmonary vascular disease and pregnancy from 1978 through 1996, Weiss and colleagues reported a maternal mortality rate of 36% in Eisenmenger syndrome, 30% in IPAH, and 56% in associated pulmonary hypertension [10]. Similarly, although acknowledging that data on outcomes are limited, previous guidelines from the American Heart Association and the American College of Cardiology recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, pulmonary hypertension, and Eisenmenger syndrome. Guidelines Recommendations In patients with PAH, suggest that pregnancy to be avoided [11, 22].

Estrogen-containing contraceptives may increase the risk of VTE and are not recommended for women with childbearing potential who have PAH. Additionally, the ETRA bosentan may decrease the efficacy of hormonal contraception. Bosentan, ambrisentan, macitentan, riociguat are contraindicated in pregnancy (category X; evidence of serious fetal abnormalities) and dual mechanical barrier contraceptive techniques are recommended in female patients of childbearing age taking these medications. When pregnancy does occur in patients with PAH, Guidelines suggest care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension, the high-risk obstetrical and cardiovascular anesthesiology services [12, 13].

3.2 Altitude and Air Travel

Exposure to high altitude (> about 1,829 m [6,000 ft] above sea level), as it may produce hypoxic pulmonary vasoconstriction and further compromise oxygen transport [25]. Supplemental oxygen should be used to maintain saturations > 91% (although firm parameters have not been established in PAH). Air travel can be problematic for patients with PAH, as commercial aircrafts are typically pressurized to the equivalent of approximately 8,000 feet above sea level. High-altitude simulation testing may be useful to more accurately determine the need for and required rate of supplemental oxygen administration during air flight [26, 27]. Guideline Recommendation In patients with PAH, we suggest that exposure to high altitude be avoided, and that supplemental oxygen be used as needed during altitude exposure or air travel to maintain oxygen saturations > 91% [25]. Patients with borderline oxygen saturations at sea level may require 3-4 L per minute of supplemental oxygen under these conditions, and those already using supplemental oxygen at sea level should increase their oxygen flow rate on commercial aircraft.

3.3 Vaccinations

Because of the potentially devastating effects of respiratory infections, immunization against influenza and pneumococcal pneumonia is recommended. Guideline Recommendation In patients with PAH, we suggest maintaining current immunization against influenza and pneumococcal pneumonia.

3.4 Surgery

Invasive procedures and surgery can be associated with increased operative and perioperative risks [28]. Patients with severe PAH are particularly prone to vasovagal events, leading to syncope, cardiopulmonary arrest, and death. Cardiac output is particularly dependent upon heart rate in this situation, and the bradycardia and systemic vasodilatation accompanying a vasovagal event can result in hypotension. Heart rate should be monitored during invasive procedures, with ready availability of an anticholinergic agent. Oversedation can lead to ventilatory insufficiency and precipitate clinical deterioration. The induction of anesthesia and intubation can be particularly problematic for patients with PAH because it can induce vasovagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure-associated changes in cardiac filling pressures. Caution should be used with laparoscopic procedures in which carbon dioxide is used for abdominal insufflation, as absorption can produce hypercarbia, which is a pulmonary vasoconstrictor. Although itself not usually a contraindication to surgery, the potential inhibitory effects of prostanoid drugs on platelet function should be noted. Guideline Recommendation In patients with PAH, we suggest avoiding non-essential surgery, and when surgery is necessary we suggest care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension team, the surgical service, and cardiovascular anesthesiology with careful monitoring and management of clinical status, oxygenation and hemodynamics postoperatively [28].

3.5 PAH with HIV patients

Several agents are available in the management of PAH in HIV (Human immunodeficiency virus) positive patients, such as endothelin receptor antagonists, prostaglandin analogs, and phosphodiesterase 5 inhibitors (PDE-5) [29]. Endothelin receptor antagonists are orally administered medications, with bosentan, sitaxsentan, ambrisentan being available on the market. Prostaglandin analog class contains parenterally administered medications such as epoprostenol and treprostinil as well as inhaled iloprost. Class of PDE-5 includes orally administered sildenafil, tadalafil, and vardenafil.

PDE-5 inhibitors block the cellular degradation of cyclic guanosine monophosphate, thereby leading to vasodilation. Several case reports were published regarding the use of sildenafil in patients with HIV-related PAH [32-34]. These case reports showed beneficial effects of sildenafil on patients' symptomatology and hemodynamic parameters. However, it is important to keep in mind the potential interactions with protease inhibitors (which are part of antiretroviral therapy) such as ritonavir and indinavir, which can increase sildenafil concentration [35]. However, Chinello *et al*. did not show any increase in adverse effects, despite the higher concentration of sildenafil in two patients with HIV-related PAH [36]. Therefore, it may be prudent to use a lower sildenafil dose in patients using protease inhibitors. To our knowledge, there are no reports regarding the use of other PDE-5 inhibitors in patients with HIV-related PAH.

Endothelin receptor blockers are an important part of PAH treatment. Sitbon *et al*. investigated the utility of bosentan in 16 patients with HIV-related PAH [37]. This study showed that bosentan therapy for 16 weeks led to an improvement in exercise capacity, quality of life, and hemodynamics as well as echocardiography variables. It is important to note that no issues regarding hepatotoxicity of bosentan were noted among patients with HIV-related PAH (this is of concern given that HIV patients are at increased risk for hepatotoxicity and bosentan is associated with abnormalities in liver function tests). Degano *et al*. studied the utility of bosentan therapy in 59 patients with HIV-related PAH [38]. Bosentan therapy was shown to be beneficial in terms of symptomatology, exercise capacity, and hemodynamics. It is important to note that both studies did not show any evidence that bosentan therapy led to worse HIV control [37, 38].

Several reports highlighted the beneficial effects of prostaglandin-based therapy of HIV-related PAH. Aguilar and Farber studied 6 patients with HIV-related PAH to assess the impact of epoprostenol therapy [39]. Follow-up cardiac catheterization showed improved hemodynamic parameters, and patients experienced a better quality of life with improvement in NYHA functional class. Cea-Calvo *et al*. showed improvements in 6-minute walk test and NYHA functional class in 3 patients with HIV-related PAH treated with treprostinil [40]. Ghofrani *et al*. enrolled 6 patients with severe HIV-related PAH to investigate the utility of inhaled iloprost [41]. These researchers showed that iloprost was associated with an improvement in the 6-minute walk test and pulmonary vascular function. A very interesting report was published in the European Respiratory Journal in 2012 [42]. The authors presented two patients in whom bosentan was successfully discontinued and no PAH recurrence was noted after 4 years of followup. The authors suggested that HIV-related PAH-specific therapy might be discontinued if the patients fulfill at least two criteria: hemodynamic normalization for at least 1 year and fully controlled HIV disease. However, their results should be replicated in larger studies prior to making any recommendations regarding the possibility of successful cessation of PAH therapies. Functional assessment with the 6 minute walk test is important to assess the functional status of

the patients [29]. Small studies of PAH-specific therapies in patients with HIV are encouraging; however, studies with a large sample size are desired to provide a robust data regarding the management of HIV-related PAH. Nevertheless, until more specific data are available, patients with HIV-related PAH should be managed in a similar manner compared to other forms of PAH.

3.6 PH with Tuberculosis patients

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition, defined as an increase in mean pulmonary arterial pressure >25 mm Hg at rest as assessed by right heart catheterization (RHC) [47]. According to the Dana Point (2008) classification of PH [48]. Group 1 PH is known as pulmonary arterial hypertension (PAH), which includes idiopathic PAH (IPAH), heritable, drug-induced and associated with PAH groups. Overall, PAH is a rare disease. Although worldwide prevalence rates are not known, overall prevalence in European countries has been reported as 15–50 cases per million population [49].

The other Groups 2-5 of PH are comparatively more common, although data are lacking. PH due to pulmonary causes, which are clubbed together as Group 3, is one of the most common causes of PH and eventually cor pulmonale. The diseases included in this group are chronic obstructive pulmonary disease, interstitial lung diseases, obstructive sleep apnea, combined emphysema and fibrosis, chronic pulmonary thromboembolism and high altitude residence [48]. Pulmonary tuberculosis (TB) has not been cited as a cause for the development of PH in western literature. In India, on the other hand, being a high burden country, it is not unusual to find patients who have been treated for pulmonary TB to present with features of right heart failure. The possible causes for the development of PH in these patients are the destruction of vascular bed due to parenchymal abnormalities, vasculitis, and endarteritis, leading to reduced cross-sectional area of the pulmonary vasculature [50, 51]. The common presentation of these patients include dyspnea out of proportion to their radiological picture, desaturation at even mild exertion and sometimes as overt heart failure with pedal edema, raised jugular venous pressure and tender hepatomegaly.

Indian data on the prevalence of PH in patients with pulmonary TB is limited [52]. It is prudent to undertake such studies, as it will be helpful in understanding the exact pathophysiology and timely intervention can be done before the development of PH, as it portends a poor prognosis.

In this issue of the journal, Bhattacharya *et al*. reported PH in patients with tuberculosis [53]. This study has its drawbacks. The number of subjects in the study is too little to generalize the results in a population. Second, it has not been mentioned whether these patients are sputum smear positive at the time of study or have been previously treated for pulmonary TB. Not using RHC for the diagnosis of PH is another shortcoming. Furthermore, functional assessment of patients should have been done through a more composite scoring system than CAT, for proper analysis.

Despite this, such studies need to be encouraged at all tertiary care centers with facilities for RHC and other relevant investigations so that nation-wide data can be collected regarding the existence of PH in treated cases of pulmonary TB. These patients present with worsening dyspnea and are incorrectly diagnosed as relapse of TB and are started on anti-TB treatment or are prescribed inhaled bronchodilators without performing spirometry or documenting airflow obstruction. It is imperative to avoid such mismanagement. Furthermore, adequate and timely management of pulmonary TB would prevent the development of PH and ultimately cor pulmonale, which significantly reduces the quality of life as well as shortens survival.

4. Conclusions

The options for pharmacotherapy in patients with PAH include several drug classes and delivery routes. The choice of therapy should be made by experienced clinicians and must be based upon an appropriately established diagnosis and evaluation of the patient's disease severity. Available evidence is sufficient to inform a limited number of strong guideline recommendation statements regarding the effect of a specific therapy or combination of therapies on select outcomes in distinct groups of patients defined according to disease severity. Where current evidence is insufficient to inform strong guideline recommendations, expert consensus may provide reasonable advice in evaluating available data and reasonable therapeutic choices. As such information and new therapies become available, a reassessment of appropriate clinical advice for the pharmacologic therapy for adult patients with PAH will be required.

5. Acknowledgements

I would like to thanks to Prof/Dr. George Cherian, HOD of Narayana Hrudayalaya Institute of Cardiac Sciences, Bangalore and Dr. Devi Shetty, Chairman of Narayana Hrudayalaya Institute of Cardiac Sciences, Bangalore for their educational supports.

6. References

1. Kiely DG, Elliot CA, Sabroe I, *et al.* Pulmonary hypertension: diagnosis and management. BMJ. 2013; 346:2028. doi: 10.1136/bmj.f2028.
2. Rich S. The current treatment of pulmonary arterial hypertension: time to redefine success. Chest. 2006; 130(4):1198-202.
3. Paramothayan NS, Lasserson TJ, Wells AU, *et al*. Prostacyclin for pulmonary hypertension in adults. Cochrane Database Syst Rev. 2005; 18(2):CD002994.
4. Reffelmann T, Kloner RA, Cardiovascular effects of phosphodiesterase 5 inhibitors. Curr Pharm Des. 2006; 12(27):3485-94.
5. Olsson KM, Hoeper MM. Novel approaches to the pharmacotherapy of pulmonary arterial hypertension. Drug Discov Today. 2009; 14(5-6):284-90. Epub
6. Toyoda Y, Thacker J, Santos R, *et al*. Long-term outcome of lung and heart-lung transplantation for idiopathic pulmonary arterial hypertension. Ann Thorac Surg. 2008; 86(4):1116-22
7. Badesch DB, Abman SH, Ahearn GS, *et al*. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004; 126(1):35S-62S.
8. Safdar Z, Pulmonary arterial hypertension in pregnant women. Ther Adv Respir Dis. 2013; 7(1):51-63.
9. McCaffrey RM, Dunn LJ. Primary pulmonary hypertension in pregnancy. Obstet Gynecol Surv. 1964; 19:567-591.
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(7):1650-1657.
11. Jais X, Olsson KM, Barbera JA, *et al.* Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir. J. 40(4):881-885.
12. Elkayam U, Dave R, Bokhari SWH. Primary pulmonary hypertension and pregnancy. In:Elkayam U, Gleicher N., eds. Cardiac Problems in Pregnancy. New York, NY: Wiley-Liss, 1998, 183-190.
13. Galiè N, Hoeper MM, Humbert M, *et al.* Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009; 34(6):1219-1263.
14. Subbaiah M, Kumar S, Roy KK, Sharma JB, Singh N. Pregnancy outcome in women with pulmonary arterial hypertension: single-center experience from India. Arch Gynecol Obstet. 2013; 288(2):305-309.
15. Badalian SS, Silverman RK, Aubry RH, Longo J. Twin pregnancy in a woman on long-term epoprostenol therapy for primary pulmonary hypertension. A case report. J Reprod Med. 2000; 45(2):149-152.
16. Monnery L, Nanson J, Charlton G. Primary pulmonary hypertension in pregnancy; a role for novel vasodilators. Br J Anaesth. 2001; 87(2):295-298.
17. O'Hare R, McLoughlin C, Milligan K, McNamee D, Sidhu H. Anaesthesia for caesarean section in the presence of severe primary pulmonary hypertension. Br J Anaesth. 1998; 81(5):790-792.
18. Stewart R, Tuazon D, Olson G, Duarte AG. Pregnancy and primary pulmonary hypertension: successful outcome with epoprostenol therapy. Chest. 2001; 119(3):973-975.
19. Decoene C, Bourzoufi K, Moreau D, Narducci F, Crepin F, Krivosic-Horber R. Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. Can J. Anaesth. 2001; 48(6):584-587.
20. Lam GK, Stafford RE, Thorp J, Moise KJ Jr, Cairns BA. Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. Obstet Gynecol. 2001; 98(52):895-898.
21. Robinson JN, Banerjee R, Landzberg MJ, Thiet MP. Inhaled nitric oxide therapy in pregnancy complicated by pulmonary hypertension. Am J Obstet Gynecol. 1999; 180(4):1045-1046.
22. Kiss H, Egarter C, Asseryanis E, Putz D, Kneussl M. Primary pulmonary hypertension in pregnancy: a case report. Am J Obstet Gynecol. 1995; 172(3):1052-1054.
23. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. Can J Anaesth. 1994; 41(6):502-512.
24. Olofsson C, Bremme K, Forssell G, Ohqvist G. Cesarean section under epidural ropivacaine 0.75% in a parturient with severe pulmonary hypertension. Acta Anaesthesiol Scand. 2001; 45(2):258-260.
25. Rubin LJ, Badesch DB. Evaluation and management of the patient with pulmonary arterial hypertension. Ann Intern Med. 2005; 143(4):282-292.
26. Roubinian N, Elliott CG, Barnett CF, *et al.* Effects of commercial air travel on patients with pulmonary hypertension air travel and pulmonary hypertension. Chest. 2012; 142(4):885-892.
27. Burns RM, Peacock AJ, Johnson MK, Church AC. Hypoxaemia in patients with pulmonary arterial hypertension during simulated air travel. Respire Med. 2013; 107(2):298-304.
28. Meyer S, McLaughlin VV, Seyfarth HJ, *et al.* Outcomes of noncardiac, nonobstetric surgery in patients with PAH: an international prospective survey. Eur Respir. J. 2013; 41(6):1302-1307.
29. McLaughlin VV. Archer SL, Badesch DB. *et al.* ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association," Journal of the American College of Cardiology, 2009; 53(17):1573-1619.
30. Fuso L, Baldi F, Di Perna A. Therapeutic strategies in pulmonary hypertension," Frontiers in Pharmacology, 2011. 2-21
31. Rubin LJ. Introduction. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines Chest, 2004. 126(7):10.
32. Schumacher YO, Zdebik A, Huonker M, Kreisel W. Sildenafil in HIV-related pulmonary Hypertension, AIDS, 2001; 15(13):1747-1748.
33. Carlsen J, Kjeldsen K, Gerstoft J. Sildenafil as a successful treatment of otherwise fatal HIV-related pulmonary hypertension, AIDS, 2002; 16(11):1568-1569.
34. Wong AR, Rasool AHG, Abidin NZ, Noor AR, Quah BS. Sildenafil as treatment for Human Immunodeficiency Virus-related pulmonary hypertension in a child. Journal of Paediatrics, and Child Health, 2006. 42(3):147-148.
35. Merry C, Barry MG, Ryan M. *et al.* Interaction of sildenafil and indinavir when co-administered to HIV-positive patients, AIDS, 1999; 13(15):101-F107.
36. Chinello P, Cicalini SS, Pichini R, Pacifici M. Tempestilli, Petrosillo N. Sildenafil plasma concentrations in two HIV patients with pulmonary hypertension treated with ritonavir-boosted protease inhibitors Current HIV Research, 2012; 10(2):162-164.
37. Sitbon O, Gressin V, Speich R. *et al.* Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension American. Journal of Respiratory. And Critical Care Medicine, 2004; 170(11):1212-1217.
38. Degano B, Yaïci A, Le Pavec J. *et al.* Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension," European Respiratory. Journal 2009; 33(1):92-98.
39. Aguilar RV, Farber HW. Epoprostenol (Prostacyclin) therapy in HIV-associated pulmonary hypertension American. Journal of Respiratory. And Critical Care Medicine, 2000; 162(5):1846-1850.
40. Cea-Calvo L, Escribano Subías P, Tello de Menesses R. *et al.* Treatment of HIV-associated pulmonary hypertension with treprostinil Revista Española de Cardiología, 2003. 56:421-425.

41. Ghofrani HA, Friese G, Discher T. *et al.* Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension European Respiratory. Journal 2004; 23(2):321-326.
42. Tcherakian C, Rivaud E, Zucman D, Metivier AC, Couderc LJ. Curing HIV-associated pulmonary arterial hypertension European Respiratory. Journal, 2012; 39(4):1045-1046.
43. Sterne 2012, Hernán MA, Ledergerber B. *et al.* Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study The Lancet, 2005; 366(9483):378-384.
44. Zuber JP, Calmy A, Evison JM. *et al.* Pulmonary arterial hypertension related to HIV infection: Improved hemodynamics and survival associated with antiretroviral therapy Clinical Infectious Diseases, 2004; 38(8):1178-1185.
    2013, http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
45. Gary-Bobo G, Houssaini A, Amsellem V. *et al.* Effects of HIV protease inhibitors on progression of monocrotaline- and hypoxia-induced pulmonary hypertension in rats," Circulation, 2010; 122(19):1937-1947.
46. D' Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM. *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991. 115:343-9.
47. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, *et al.* Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009. 54(1)Suppl: S43-54.
48. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. Eur Respir. J 2007. 30:104-9.
49. Ferrer MI. Cor pulmonale (pulmonary heart disease): Present-day status. Am Heart. J 1975; 89:657-64.
50. Fishman AP. State of the art: Chronic cor pulmonale. Am Rev Respir Dis 1976; 114:775-94?
51. Kapoor SC. Pulmonary hypertension in pulmonary tuberculosis. Indian. J Tuberc. 1950; 6:50-64.
52. Bhattacharyya P, Saha D, Bhattacherjee PD, Das SK, Bhattacharyya PP, Dey R. Tuberculosis associated pulmonary hypertension: The revelation of a clinical observation. Lung India 2016; 33?-?