Case Report

Stage IV Sarcoidosis with Cor pulmonale: A Case Report

Mostashirul Haque[1], Tunaggina Afrin Khan[1], Md Rasul Amin[2], Montasin Rezwan[1], Md. Rashidul Hasan[3], KMHS Sirajul Haque[1], H I Lutfur Rahman Khan[1].

Abstract:

Sarcoidosis is a well known systemic disorder that invariably involves lungs. However, pulmonary hypertension and cor-pulmanle are not common due to pulmonary involvement of sarcoidosis. We report a case of pulmonary hypertension leading to corpulmonale due to sarcoidosis. An elderly female suffering from hypertension & sarcoidosis developed complications and arrived at the diagnosis by correlating various investigations. X-ray chest (P/A) showed cardiomegaly (right ventricular type), reticulo-nodular shadow involving both mid and lower zone; characteristic high resolution CT (HRCT) scan appearances include reticulonodular opacities; pulmonary function test showed restrictive type of defect; ECG showed right ventricular hypertrophy with strain pattern; in echocardiogram there were right ventricular hypertrophy (RVH) with pulmonary artery systolic pressure (PASP) of 63 mmHg indicating severe pulmonary arterial hypertension (PH); along with significantly elevated B-type natriuretic peptide(BNP) level.

(Bangladesh Heart Journal 2015; 30(1) : 37-42)

Introduction:

Pulmonary hypertension can have a very insidious onset & hard to notice for both patients & doctors. As it cannot be diagnosed on clinical grounds alone & requires detailed investigation, it is often diagnosed late; when useful therapeutic options may be limited. It may take up to two years to diagnose the condition though it can progress very quickly in some cases, it demands significant challenges in terms of early detection.[1]

Case summary:

In February, 2015, a 67 years old female got admitted at the hospital with the complaints of progressively increased breathlessness from NYHA class 1-2 for 1 month to NYHA class 3-4 for 7 days prior to admission which made her bed bound. It was associated with orthopnea but there was no history of PND or any exacerbating factors like exposure to dust, mites, pollen or drug. She gave a history that she had been a diagnosed case of sarcoidosis for last 7-8 years, while she experienced mild degree of self limiting shortness of breath. She also noted non productive cough which became severe in the last seven days. On further questioning she also revealed history of gradual weight loss associated with loss of appetite but she denied any H/O chest pain, fever, night sweat or hemoptysis. On examination, She was well oriented, alert, co-operative, intelligent with average body built and good nutritional status but she was mildly anemic, edematous, dypnoeic and was in propped up position. Her JVP was raised to 12 cm of H_2O at 45 degree angle with prominent a wave. BP was 130/70 mm Hg, pulse was 84 beats/min, regular. Her precordium was bulged; apex beat was felt in 5^{th} intercostal space 11 cm lateral to midline, lateral to mid clavicular line. There was palpable P2 and left parastenal heave. First heart sound was soft; pulmonary component of the second heart sound was loud. There was a pansystolic, grade 3/6 murmur, soft blowing in nature in left lower parasternal area better audible in breath held in inspiration. Her RR was 30/min, movement of the chest was symmetrically diminished to 4 cm, use of accessory muscles was prominent and there was intercostal and subcostal recession. Vocal fremitus and vocal resonance were increased in mid and lower zone. Percussion note was dull; coarse end inspiratory crepitations were heard

1. Department of Cardiology, Anwer Khan Modern Medical College & Hospital, Dhaka. E-mail: mustashir.haque@yahoo.com
2. Department of Cardiology, Bangabandhu Sheikh Mujib Medical University
3. Department of Chest Medicine, National Institute of Chest Disease Hospital, Dhaka.

especially in mid and lower zones of the chest on both sides. There was no organomegaly.

Her baseline investigations showed mild anemia, mild renal impairment, hyperurecemia along with significantly elevated BNP level (10,252 pg/ ml) with hymphopenia (15%). ABG-analysis was normal. Liver function and Thyroid function test were normal. Tuberculin skin test was negative and nucleic acid amplification test for detection of both tubercular DNA and rifampicin resistance was also negative. Lung function test revealed restrictive pattern and 6 minute walk test showed moderate exercise tolerance.

X-ray chest (P/A) showed cardiomegaly (right ventricular type), bilateral bronchovascular accentuation was noted. Right pulmonary artery (PA) was dilated which contrasts with peripheral pruning of blood vessel. Reticulo rodular opacities with honey comb shadows were also seen in both mid and lower zone (Figure 1).

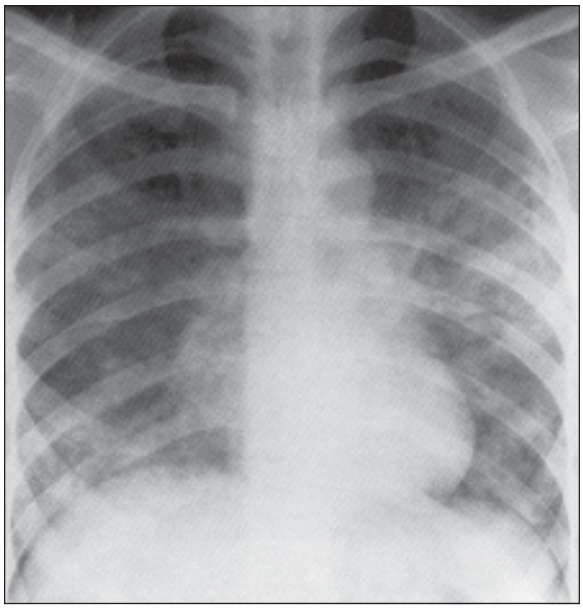


Fig.- 1:

ECG showed complete right bundle branch block with right ventricular hypertrophy with strain, right axis deviation, right atrial enlargement (Figure 2).

Echocardiography, revealed enlargement & hypertrophy of RV with dilated RA & PA, with grade-I diastolic dysfunction, moderate to severe tricuspid regurgitation with PASP 63 mm Hg (figure 3)

CT scan of thorax showed reticulonodular opacities with diffuse central ground glass opacification and thickening of interlobular septa (figure 4).

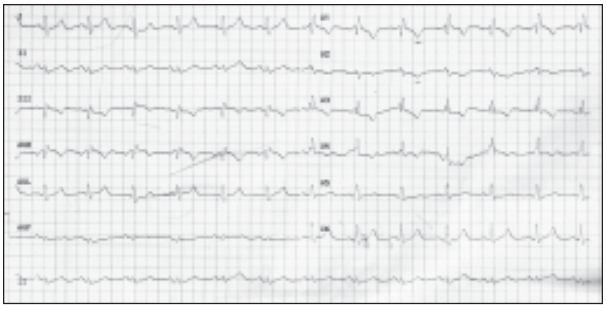


Fig.- 2:

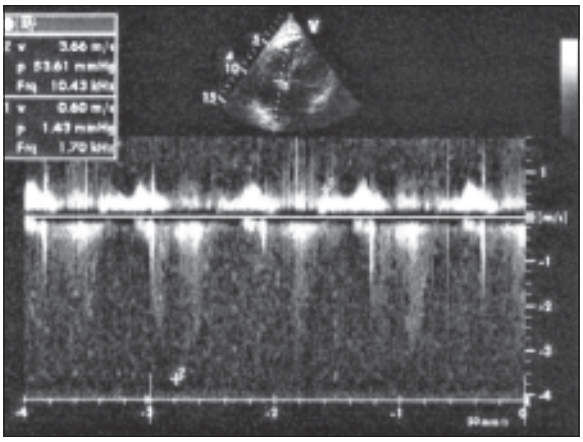


Fig.- 3:

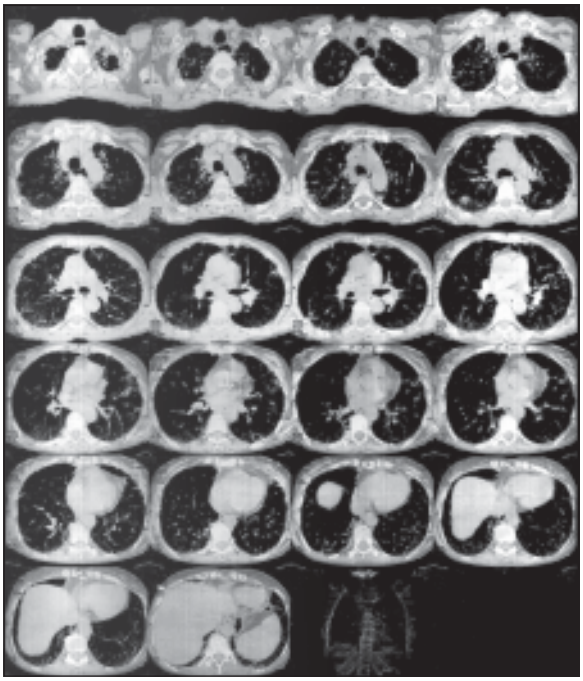


Fig.- 4:

She was treated with furosemide, amlodipine, enoxaparin, bosentan, intravenous methylprednisolone followed by oral prednisolone and methotrexate. She was discharged two weeks after hospitalization and she came for further follow up after one month with significant symptomatic relief. Intensity of tricuspid regurgitation was found only mild to moderate with PASP 45 mm Hg.

Discussion:

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological state that can be found in multiple clinical conditions which have been classified into six diagnostic groups with specific histological, clinical and therapeutic features.[1-3]

Updated clinical classification of pulmonary hypertension[1-3]*:*

1. Pulmonary arterial hypertension.
   - 1.1- Idiopathic
   - 1.2- Heritable
   - 1.3- Drugs and toxins
   - 1.4- Associated
1. Pulmonary veno-occlusive disease.
2. Pulmonary hypertension due to left heart disease.
3. Pulmonary hypertension due to lung disease or hypoxia.
4. Chronic thromboembolic pulmonary hypertension.
5. Pulmonary hypertension unclear multifactorial mechanisms.

Clinical suspiction of PH should arise in any case of breathlessness without overt signs of specific heart or lung diseases.The symptoms of PH can also include fatigue, angina, syncope and abdominal distension. Symptoms at rest are reported only in very advanced cases. The physical signs of PH may require experience to appreciate. They include LPL, accentuated P2, PSM of TR, EDM of PR and RV S3. Jugular venous distension, hepatomegaly, peripheral edema, ascites and cool extremities characterize patients in a more advanced state with RVF at rest. Central cyanosis may also be present.[1-3]

Finally, PH can be suspected when abnormal ECG, Chest-X ray or echocardiographic findings, are detected in course of procedures performed for other clinical reasons.

ECG: RVH on ECG is present in 87% and RAD in 79% of patient with PH.[3] Chest X-ray: In 90% of PH patient is abnormal. Findings are central PA dilation which contrasts with pruning of the peripheral blood vessels. RA and RV enlargement may be seen and it progresses in more advanced cases. Transthoracic doppler echocardiography: is an excellent non-invasive screening test for the patient with suspected PH. Although invasive measurement of pulmonary pressure is considered to be gold standard, it is not routinely recommended due to its invasive nature. Therefore, echocardiography has become a useful non-invasive technique for estimating the PASP using the Doppler derived velocity of the TR jet. Pulmonary hypertension is defined as PASP >35 mm Hg & patients are categorized according to the following categories: Non measurable, normal PASP < 35mm Hg, mild (PASP: 36-45 mm Hg), moderate (PASP: 46-60 mm Hg), severe PH (PASP >60 mm Hg).

Patients with severe PH showed a higher cumulative incidence of CV mortality. Compared to those patients with normal PASP, only patients with severe PH (PASP >60 mm Hg) showed an adjusted increased of risk of 1 year cardio vascular mortality[1-5].

There is an evidence based treatment algorithm that is intended to provide a guide to the selective use of each form of therapy. Exercise should be limited to a symptom free level. Physical activities after meals/in extreme temperature should be avoided. Appropriate adjustments of daily activities may improve quality of life & reduce frequency of symptoms.

Travel/attitude- Hypoxia may aggravate vasoconstriction in PAH patients & avoid mild degree of hypoxia that starts at attitudes between 1500 & 2000 m. Commercial airplanes are pressurized to equivalent attitude between 1600 & 2500 m & supplemental O_2 should be considered. *Prevention of infections* in patients with PAH are susceptible to develop pneumonia that is the cause of

PAH: Determinants of prognosis:(ACCF/AHA 2009expert consensus document on pulmonary hypertension).[6]

Determinants of risk	Lower risk (good prognosis)	Higher risk (poor prognosis)
Clinical evidence of RV failure	No	Yes
WHO class	II, III	IV
6 MW distance	longer (>400 meter)	Shorter (<300 meter)
CPET (Cardio pulmonary exercise testing)	Peak VO_2>10.4 ml/kg/min	Peak Vo_2<10.4ml/kg/min
Echo	Minimum RV dysfunction	Pericardial effusion, sign of RVE (dysfunction), RAE.
Hemodynamics	RAP< 10 mm Hg , CI>2.5 l/min/m^2	RAP > 20, CI < 2.0 l/min/m^2
BNP	Minimally elevated	Significant elevated

death in 7% cases.[3,7] Pulmonary infections are poorly tolerated & need to be promptly recognized & treated. Vaccine strategies are recommended for influenza & pneumococcal pneumonia. Pregnancy associated with increased rate of deterioration & death (Mortality of 30-50%).[3] AHA & ACC Guideline recommended that pregnancy be avoided /terminated.

Haemoglobin level: Patients PAH are highly sensitive to reductions in Hb levels. Any kind of mild anaemia should be promptly treated. Patients with long standing hypoxia (e.g. R ®L shunts) tend to develop erythrocytosis with elevated levels of hematocrit (Phlebotomies are indicated if HCT is above 65%). Concomitant medications-Emperic use of ACE inhibitor & beta blocker for chronic biventricular heart failure should be discouraged.[3]

Pharmacological treatment:

1. *Oral anticoagulant*: The rationale for the use in patients with PAH is thrombotic changes in the pulmonary microcirculation & in the elastic PA.[7,8] This practice is supported by the high incidence of ante mortem clots found at autopsy in the small pulmonary artery and arterioles of patient with PAH.[8]

2. *Diuretics*: In case of RHF allows clear symptomatic & clinical benefits.[3]

3. *Calcium channel blocker (CCB*): Only about half of IPAH positive acute responders (defined as a reduction of mean PAP >10 mm Hg to reach an absolute value of mean PAP < 40 mm Hg with an increase or unchanged cardiac output, done using short acting pulmonary vasodilator I.V PGI_2, or adenosine & inhaled nitric oxide at the time of right heart catheterization) are also positive long term responders to CCB & only in these case the continuation of CCB as single treatment is warranted.[3,9]

4. *Digitalis*: Short term I.V administration produces & modest increase in cardiac output & significant reduction of circulating nor-epinephrine levels; however no data are available on the effects of long term treatment. It may be used in the rare PAH patients with atrial fibrillation (AF) or atrial flutter (AFL) to slow ventricular rate.[3]

5. *Synthetic prostacyclin & prostacyclin analogues*: PGI_2 is produced predominantly by endothelial cells has a vasodilatory and anti-proliferative activities.It is also a potent inhibitor of platelet aggregation. Epoprostenol(IV): Improves symptoms, exercise capacity & hemodynamics. Treprostinil, (S.C) – reduce symptom of dyspnea associated with exercise. IIoprost inhalation: the study showed an increase in exercise capacity & improvements of symptoms, PVR & clinical events. Beraprost- Beraprost is a first chemically stable and orally active prostacyclin analogue. Two randomized controlled studies with this compound have shown an improvement in exercise capacity that unfortunately oersists only up to 3-6 months.[5,8,10]

6. Type 5 phosphodiesterase inhibitors: Sildenafil(20 mg TDS) and tadalafil (40 mg once daily) increase tissue levels of cGMP which causes smooth muscle relaxation and vasodilation. Sildenafil causes significant improvements in 6-minute walk distance and hemodynamics in patient with PAH.[7] Tadalafil is an OD dosing, selective PDE-5 inhibitor. A pivotal randomized controlled trial on 406 PAH patients treated with tadalafil 5, 10, 20 or 40 mg OD has shown favorable results on exercise capacity, symptoms, haemodynamics, and time to clinical worsening for the largest dose.[3,11]

7. Endothelin 1 receptor antagonist: Three ERAs, bosentan, ambrisentan and macitentan are currently commercialy available for the treatment of PAH.

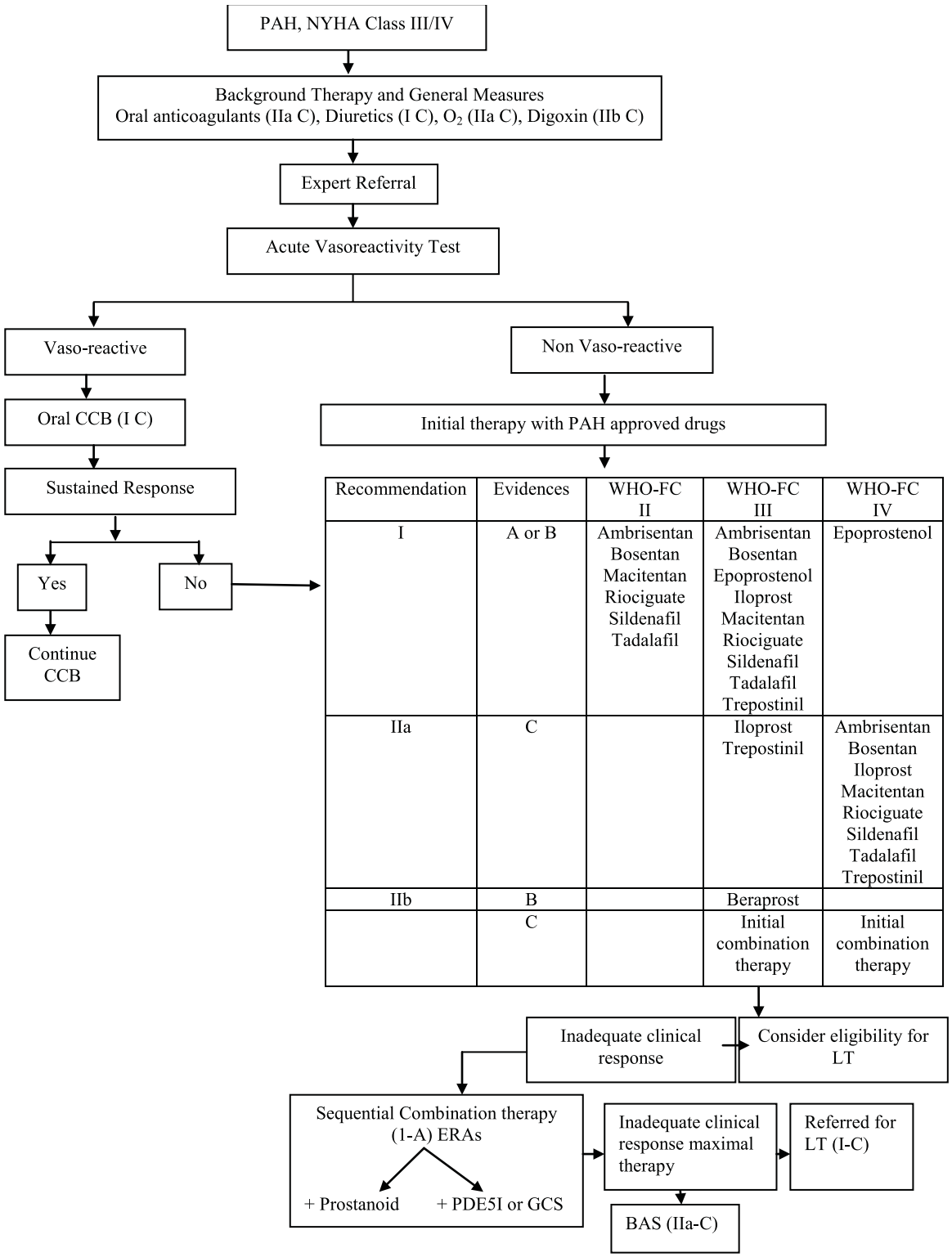
Dual antagonists-*bosentan and macitentan* which affect both ET_A and ET_B receptors. Bosentan orally active dual ET_A & ET_B receptor antagonist,a non selective ET receptor blocker has produced an improvement in 6 minute walk distance.[6] Dose of bosentan : 62.5 mg twice daily for 4 weeks followed by 125 mg bid for minimal 12 weeks. Increases in hepatic aminotransferases occurred in 10% of the subjects.[8] This hepatic impairment is dose dependent and reversible after dose reduction or discontinuation. Macitentan has been studied in phase III long term morbidity & morality trial in which primary endpoint was time from initiation of treatment to first occurrence of composite endpoint of death, BAS,lung transplantation, initiation of treatment parental prostanoids or worsening PAH. 742 patients were randomly assigned to either placebo; macitentan 3 mg; macitentan 10 mg daily. There was a 30% & 45% risk reduction in the primary endpoint with the 3 mg & 10 mg doses respectively. Selective ET_A receptor antagonists-Ambrisentan , has been in evaluated in a pilot study and a two large randomized controlled trials which have demonstrated efficacy on symtomps, exercise capacity, haemodynamics and time to clinical worsening.[11] Ambrisentan has been approved also for the treatment of WHO/NYHA –FC II patients. The current approved dose 5 mg OD. Increase hepatic aminotranseferase is less in this selective ET_A-receptor blocker than besentan.[3]

8. Soluble Guanylate cyclase stimulator : Riocuguate is a first in class agent that directly stimulates soluble guanylate cyclase independent of NO. In a 12 week, multicenter open label, uncontrolled phase II trial in patients with PAH & CTEPH, riociguate improve 6 MW distance & haemodynamics. Riociguate should not be used concurrently with PDE5I. [12]

Interventional Procedures:

Balloon atrial septostomy (BAS): At present it is indicated for advanced NYHA class III and class IV patients with recurrent syncope or RHF despite all available medical

Evidence based treatment algorithm[13,14]:



treatments or as a palliative bridge to lung transplantation. *Lung transplantation*: indicated PAH with advanced symptoms that is refractory to available medical treatments. The 3 and 5 year survival after lung and heart-lung transplantation is approximately 55% and 45% respectively.[3]

Conclusion:

PH is a serious complication of sarcoidosis. It is common in patients with advanced disease. Patients who complain of persistent dyspnoea should be screened for the presence of PH. Echocardiogram is a good initial screening tool in the diagnosis of PH. RHC is to make the diagnosis. Clinicians must be vigilant for the development of sarcoidosis-associate pulmonary hypertension (SAPH) since this complication appears to be associated with worse outcomes. Prompt recognition and referral to an experienced center for consideration of initiation of specific therapy or transplant evaluation are important considerations.

References:

1. Galie N, Hoeper MM, Humbert M et al. the task force for the diagnosis & treatment of PH of the European society of cardiology & the European respiratory society, endorsed by international society of the Heart & Lung transplantation (ISHLT). Eurr Heart J 2009;30:2493-2537.
2. Simonneau G, Robbins I, Beghetti M et al. Updated clinical classification of PAH. J Am Coll Cardiol 2009; 54:543-554.
3. Galie N, Torbicki A, Barst R et al.The task force on diagnosis and treatment of pulmonary arterial hypertension of the European society of cardiology. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. Eurr Heart J 2004; 25: 2243-2278.
4. Galie N, Ghofrani HA,Torbicki A et al: Sildenafil citrate therapy for PAH. N Eng J Med 2005; 353:2148.
5. Galie N, Manes A, Branzi A. Prostanoids for pulmonary arterial hypertension. Am J Respir Med 2003;2:123-137.
6. McLaughlin VV, Archer SL, Badesch DB, et al; ACCF/AHA.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. *J Am Coll Cardiol 2009; 53: 1573-1619.*
7. Galie N, Brundage B, Ghofrani A et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119:2894-2903.
8. Barst RJ, Rubin LJ, Long WA et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The primary pulmonary hypertension study group. N Engl J Med 1996;334:296-302.
9. Baughman RP, Carbone RG, Bottino G. Pulmonary arterial hypertension & ILD: A Clinical guide. Springer 2009; 226-230.
10. Barst RJ, Galie N, Naieje R, Simonneau G et al. Long term outcome in pulmonary arterial hypertension patients treated with subcutaneous trepostinil. Eur Respir J 2006;20:1195-1203.
11. Galie N, Badesch BD, Oudiz R et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005; 46: 529-536.
12. Ghofrani HA, Hoeper MM, HAlank M, et al. Riociguate for chronic thromboembolic PH and PAH. A phase II study. Eur Respir J 2010; 36: 792.
13. Barst RJ, Gibbs SR, Ghofrani HA et al. Updated evidence-based treatment algorithm in PAH. J Am Coll Cardiol 2009; 54: S78-S84.
14. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl): D60-72.