Pulmonary arterial hypertension is a progressive, symptomatic, and ultimately fatal disorder. It can be simply defined as a syndrome characterized by high pulmonary pressure due to an elevated precapillary pulmonary resistance.\(^1\)\(^3\) Pulmonary hypertension is deemed present when the mean pulmonary artery pressure exceeds 25 mm Hg at rest, or 30 mm Hg with exercise. The presence of pulmonary arterial hypertension further requires normal left heart filling pressures (i.e., a normal left ventricular end diastolic pressure directly measured, or indirectly approximated by a pulmonary artery occlusion pressure less than 15 mm Hg).

Pulmonary hypertensive disorders are classified into groups on the basis of underlying mechanism, presentation, clinical context, histopathology, and response to treatment (Table I).

**Clinical Classification of Pulmonary Hypertension\(^1,2\)**

**Epidemiology of Pulmonary Arterial Hypertension**

Idiopathic PAH is a rare disease, with an estimated incidence of one to two cases per million. National Institutes of Health (NIH) established the prospective National Registry for the Characterization of Primary Pulmonary Hypertension.\(^4\)\(^5\) One hundred eighty-seven patients from 32 centers were enrolled between 1981 and 1985. The disease affected all ages, both men and women, and many ethnic groups. The mean age of patients in the Registry was 36.4 years, similar for women and men. Women were affected more frequently, however, with a female to male ratio of 1:1. Nine percent of patients were older than 60.

**Diagnosis of Pulmonary Arterial Hypertension**

The symptoms associated with PAH are nonspecific and often are confounded by the presence of comorbid conditions that might explain them. Dyspnea (particularly with exertion) is the most common initial complaint (60%), followed by fatigue (19%), syncope (8%), chest pain (7%), near syncope (5%), palpitations (5%) and leg edema (3%). Idiopathic pulmonary arterial hypertension
(IPAH) presentations occur more often in young women, often with normal examinations early in their course.

Cardiac auscultation may reveal an accentuated pulmonic component of the second heart sound along the delayed closure of the pulmonic valve (split “S2”) in up to 90% of patients who have IPAH. Other signs may include a palpable left parasternal heave, a right ventricular S3 or S4 gallop, prominence of the jugular “a” wave or “v” wave, hepatojugular reflux, and lower extremity edema. A variety of murmurs also may be encountered on cardiac auscultation; including the high-pitched holosystolic murmur of tricuspid regurgitation heard best at the lower left sternal border or the early diastolic high pitched Graham Steel murmur of pulmonic regurgitation.

Considering the diverse etiologies a detailed work up is mandatory in a patient with pulmonary hypertension. Table 2 summarizes relevant diagnostic evaluation in a patient of PAH

**EVALUATION OF SEVERITY**

The evaluation of severity of patients with PAH takes place between the diagnostic process and the therapeutic decision-making. Both clinical and hemodynamic assessments yield important prognostic information that may guide clinical management. A number of adverse prognostic determinants has been identified such as evidence of heart failure, rapid rate of progression of symptoms, history of syncope, advanced WHO functional class, <300m six minute walk distance, very high and rising BNP levels, Pericardial effusion on echo, right atrial pressure more than 15mmHg and reduced cardiac output on cardiac catheterization etc.10,11

**THERAPY**

In the past few years, treatment of PAH has undergone an extraordinary evolution, which has led to the current approval by regulatory agencies of eight drugs with different routes of administration. In addition, a meta-analysis performed on 23 RCTs in PAH patients reports a 43% decrease in mortality and a 61% reduction in hospitalizations in patients treated with specific drug therapies vs. patients randomized to placebo.12

**General measures:** These are strategies to limit the exposure of patients to factors that may aggravate pulmonary hypertension related symptoms.

- Physical activity and supervised rehabilitation: avoiding excessive physical activities.
- Pregnancy poses extremely high risks for the woman with PAH and her fetus. Such women should prevent pregnancy through sterilization or dual-contraceptive methods.
- Travel: Hypoxemic patients should avoid air travel and visits to sites at high altitudes.
- Infection prevention: Pulmonary infections need early attention and prompt treatment. Vaccination against influenza and pneumococcus pneumonia is recommended.

**SUPPORTIVE THERAPY**

Oral anticoagulants Currently, it is a widely accepted practice to use anticoagulation in patients who have PAH (WHO group I) unless there is a contraindication.

Diuretics The use of diuretics in patients who have PAH with peripheral edema secondary to right heart failure is widespread and universally accepted.

Oxygen supplementation: Beneficial in hypoxemic patients

Digoxin may be useful for inotropic support in patients with right ventricular dysfunction and failure. Its role in PAH still remains unproven.

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**Table 2 : Diagnostic evaluation in a case of pulmonary artery hypertension [pulmonary artery hypertension (PAH), right ventricle (RV)]**

<table>
<thead>
<tr>
<th>Required studies</th>
<th>Pertinent Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>Signs of PAH and evidence of right heart failure</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Enlargement of central pulmonary arteries reflects level of PA pressure and duration</td>
</tr>
<tr>
<td></td>
<td>Peripheral pruning</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Right axis deviation</td>
</tr>
<tr>
<td></td>
<td>RV hypertrophy and strain</td>
</tr>
<tr>
<td></td>
<td>Right atrial enlargement</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Evidence of PAH</td>
</tr>
<tr>
<td></td>
<td>RV function</td>
</tr>
<tr>
<td></td>
<td>Left heart valvular or (systolic or diastolic) myocardial disease</td>
</tr>
<tr>
<td></td>
<td>Shunt lesions (congenital heart disease)</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>Obstructive or restrictive lung disease</td>
</tr>
<tr>
<td>Ventilation Perfusion lung scan</td>
<td>Rule out vascular obstruction (Chronic Thromboembolic PAH)</td>
</tr>
<tr>
<td>Anti nuclear antibody assay</td>
<td>Screen for connective tissue disease associated PAH</td>
</tr>
<tr>
<td>HIV test</td>
<td>Screen for HIV associated PAH</td>
</tr>
<tr>
<td>Liver function test</td>
<td>Screen for liver disease associated PAH</td>
</tr>
<tr>
<td>BNP</td>
<td>Measure of RV failure</td>
</tr>
<tr>
<td>Overnight oxymetry</td>
<td>Screen for sleep disorder/nocturnal desaturation</td>
</tr>
<tr>
<td>6 minute walk test</td>
<td>Prognostic estimate</td>
</tr>
<tr>
<td>Hemodynamic right heart catheterization</td>
<td>Assessment of right atrial, pulmonary artery and pulmonary capillary wedge pressures, cardiac output etc</td>
</tr>
<tr>
<td>with short acting vasodilator testing</td>
<td>Response to short acting vasodilator (likelihood of responding to calcium channel blocker treatment)</td>
</tr>
<tr>
<td>Additional tests like transesophageal echo, contrast and high resolution CT, polysomnography, pulmonary angiography may be done in indicated cases. Lung biopsy is rarely advisable because of risk</td>
<td></td>
</tr>
</tbody>
</table>

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SPECIFIC DRUG THERAPY

No current treatment approach to PAH provides a cure. Rather, treatment goals are to reduce pulmonary vascular resistance, pressure, and symptoms and to increase patient activity and longevity. Four classes of medications are available that act on the predominant recognized pathobiologic pathways.

CALCIAL CHANNEL BLOCKERS (CCB):

Rationale: Calcium channel blockers reduce the influx of calcium ions into pulmonary arterial smooth muscle cells, thereby reducing calcium-mediated activity of the contractile mechanism.

Patients who exhibited the ability to vasodilate in response to short-acting agents, such as adenosine, the use of calcium channel blockers has shown to provide substantial survival benefit.

The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two. The choice of CCB is based on the patient’s heart rate at baseline, with a relative bradycardia favoring nifedipine and amlodipine and a relative tachycardia favoring diltiazem. The daily doses of these drugs that have shown efficacy in IPAH are relatively high, 120–240 mg for nifedipine, 240–720 mg for diltiazem, and up to 20 mg for amlodipine. It is advisable to start with a low dose, e.g. 30 mg of slow release nifedipine twice a day, 60 mg of diltiazem three times a day, or 2.5 mg of amlodipine once a day and increase cautiously and progressively to the maximum tolerated dose. Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral edema. Patients with IPAH who meet the criteria for a positive vasodilator response and are treated with a CCB should be followed closely for both safety and efficacy with an initial reassessment after 3–4 months of therapy including RHC.

PROSTANOIDS

Rationale: Prostacyclin, a metabolite of arachidonic acid that is produced in the vascular endothelium, inhibits platelet aggregation and is a potent pulmonary vasodilator. In patients with PAH, a relative deficiency of prostacyclin occurs because of down-regulation of prostacyclin synthase. Prostacyclin analogues supplement deficient levels of prostacyclin.

Administering prostanooids has been a mainstay of PAH therapy for more than a decade. There are currently 4 commercially available prostanooids: epoprostenol, treprostinil iloprost and beraprost.

Epoprostenol: Intravenous epoprostenol improves functional class, exercise tolerance, hemodynamics, and survival in IPAH. An open label, randomized trial of 81 functional class III and IV IPAH patients demonstrated significant improvements in the primary end point of 6MW test and in secondary end points including hemodynamics and quality of life. Longer-term observational studies have confirmed the chronic benefits of intravenous epoprostenol in IPAH patients.

Epoprostenol must be delivered by continuous intravenous infusion. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. Intravenous epoprostenol is commonly started in the hospital at a dose of 2 ng/kg/min and the dose is further adjusted up based on symptoms of PAH and side effects of the drug. While the dosing must be highly individualized, most experts believe that the optimal dose range for chronic therapy is between 25 and 40 ng/kg/min for most adult patients, when used as monotherapy. Chronic overdose sometimes results in high cardiac output failure, and the long-term consequences of this are unknown and may be detrimental.

Common side effects include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions (due to rebound severe PAH) can be life-threatening. Given its considerable complexity, epoprostenol use should be limited to centers experienced with its administration and with systematic follow-up of patients.

Treprostinil: Treprostinil is a stable prostanoid with an elimination half-life of about 4.5 hours that was first studied using subcutaneous administration during a 12-week, placebo controlled, multicenter, randomized trial of 470 patients with functional class II, III, or IV PAH subcutaneous treprostinil resulted in a modest but statistically significant between treatment group median increase of 16 m of the 6MW test, which was dose related. The change in 6MW test was a result of improvement in the group receiving treprostinil, and there was no change in 6MW test in the placebo group.

Adverse effects included pain or erythema at the site of the subcutaneous infusion in 85% of patients. Other common side effects include headache, diarrhea, rash, and nausea. Given the complexity of administration of both intravenous and subcutaneous treprostinil, administration should be limited to centers with experience with this agent.

Iloprost is a prostanoid that can be delivered by an adaptive aerosol device that has been studied in a 12-week, multicenter, placebo-controlled, randomized trial of 207 functional class III and IV patients with either IPAH, PAH associated with scleroderma spectrum of diseases or appetite suppressants, or PH related to inoperable chronic thromboembolic disease. Common side effects of inhaled iloprost include cough, headache, flushing, and jaw pain. Iloprost is approved by the FDA for functional class III and IV PAH in 2004.

Beraprost is an orally active prostacyclin analogue. In the ALPHABET trial beraprost improved exercise capacity and symptoms over a 12-week period but had no significant effect on cardiopulmonary hemodynamics or functional class. However, these improvements were not sustained in another study where patients were followed up for 1 year.

ENDOTHELIN RECEPTOR ANTAGONISTS

Rationale: Elevated endothelin levels resulting from enhanced
production and reduced pulmonary clearance has been found in patients of PAH. Endothelin receptor antagonists block the effect of endothelin at smooth muscle cell receptors

**Bosentan.** Bosentan is an oral active dual endothelin-A and endothelin-B receptor antagonist and the first molecule of its class that was synthesized. Bosentan has been evaluated in PAH (idiopathic, associated with CTD and Eisenmenger’s syndrome) in five randomized controlled trials (Pilot, BREATHE-1, BREATHE-2, BREATHE-3, and BREATHE-5) that have shown improvement in exercise capacity, functional class, haemodynamics, echocardiographic and Doppler variables, and time to clinical worsening.11-24

Two randomized controlled trials have enrolled exclusively patients with WHO-functional class II or patients with Eisenmenger’s syndrome. This has resulted in regulatory authority approval for the use of bosentan in the treatment of PAH patients in WHO functional class II and also in patients with PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger’s syndrome. Bosentan treatment is started at the dose of 62.5 mg twice daily and up titrated to 125 mg twice daily after 4 weeks.

Long-term observational studies have demonstrated the durability of the effect of bosentan in adult IPAH patients over time. Increases in hepatic aminotransferases occurred in 10% of the subjects but were found to be dose dependent and reversible after dose reduction or discontinuation. For these reasons, liver function test should be performed monthly in patients receiving bosentan. Reductions on hemoglobin levels and impaired spermatogenesis have also been observed.

**Sitaxentan:** Sitaxentan, a selective orally active endothelin-A receptor antagonist, has been assessed in two RCTs (STRIDE I and 2) on patients with WHO-FC II and III PAH. The studies demonstrated improvements in exercise capacity and haemodynamics. A 1-year, open-label observational study has demonstrated the durability of the effects of sitaxentan over time.25

**Ambrisentan:** Ambrisentan is a non-sulfonamide, propanoic acid class, ERA that is selective for the endothelin-A receptor. Ambrisentan has been evaluated in a pilot study and in two large RCTs (ARIES I and 2), which have demonstrated efficacy on symptoms, exercise capacity, haemodynamics, and time to clinical worsening of patients with IPAH and PAH associated with CTD and HIV infection.26

Ambrisentan has been approved for the treatment of WHO functional class II and III patients. The current approved dose is 5 mg once daily that can be increased to 10 mg once daily when the drug is tolerated at the initial dose.

**PHOSPHODIESTERASE TYPE-5 INHIBITORS**

**Rationale:** Decreased nitric oxide synthase expression has been found in PAH. Phosphodiesterase 5 (PDE5) inhibitors promote the activity of the nitric oxide pathway by reducing conversion of cyclic guanylate monophosphate (a second messenger) to 5’-guanylate monophosphate (an inactive product). Since the pulmonary vasculature contains substantial amounts of phosphodiesterase type-5, the potential clinical benefit of phosphodiesterase type-5 inhibitors has been investigated in PAH. In addition, phosphodiesterase type-5 inhibitors exert antiproliferative effects.

**Sildenafil.** Sildenafil is an orally active, potent, and selective inhibitor of phosphodiesterase type-5. A number of uncontrolled studies have reported favourable effects of sildenafil in IPAH, PAH associated with connective tissue disease and chronic thromboembolic pulmonary hypertension.

An RCT (SUPER-1) on 278 PAH patients treated with sildenafil 20, 40, or 80 mg three times a day (t.i.d.) has confirmed favourable results on exercise capacity, symptoms, and haemodynamics.27 The approved dose is 20 mg t.i.d., but the durability of effect up to a year has been demonstrated only with the dose of 80 mg t.i.d. In clinical practice, up-titration beyond 20 mg t.i.d. (mainly 40–80 mg t.i.d.) is needed quite frequently.

**Tadalafil.** Tadalafil is a once-daily dispensed, selective phosphodiesterase type-5 inhibitor, currently approved for the treatment of erectile dysfunction. An RCT (PHIRST) on 406 PAH patients (50% on background bosentan therapy) treated with tadalafil 5, 10, 20, or 40 mg once daily has shown favourable results on exercise capacity, symptoms, haemodynamics, and time to clinical worsening at the largest dose.28 The durability of the effect has also been shown. The side effect profile was similar to that of sildenafil.

**EXPERIMENTAL COMPOUNDS AND ALTERNATIVE MEDICAL STRATEGIES**

Despite the progress on the treatment of PAH, the functional limitation and the survival of these patients remain unsatisfactory. For these reasons, additional therapeutic strategies targeted to diverse pathobiological changes are being explored in order to improve symptoms and prognosis further.

Phase II and III studies are currently being performed with the following compounds: NO-independent stimulators and activators of cGMP, inhaled vasoactive intestinal peptide, non-prostanoid prostacyclin receptor agonists, tissue dual ERA-, tyrosine kinase inhibitors (platelet-derived growth factor inhibitors), and serotonine antagonists. The following additional compounds are in an earlier stage of development: rho-kinase inhibitors, vascular endothelial growth factor receptor inhibitors, angiopoietin-1 inhibitors, and elastase inhibitors.

Gene therapy strategies have been tested in animal models. Stem cell therapy has proven to be effective in the monocrotalin rat model and is currently being tested in proof-of-concept and dose-finding studies in PAH patients.
COMBINATION THERAPY
The term combination therapy describes the simultaneous use of more than one PAH specific class of drugs, e.g. endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, prostanoids, and novel substances. Combination therapy has become the standard of care in many PAH centers, although long-term safety and efficacy have not yet been amply explored.

Results of a few RCTs evaluating combination therapy for PAH have been published. The relatively small BREATHE-2 study showed a trend to a better hemodynamic effect of the initial combination epoprostenol-bosentan as compared to epoprostenol alone. The STEP-I study addressed the safety and efficacy of 12 weeks therapy with inhaled iloprost in addition to bosentan and found a marginal increase in the post-inhalation 6 min walk distance. In contrast, another RCT, COMBI, which also studied the effects of inhaled iloprost added to bosentan, was stopped prematurely after analysis did not show an effect on 6 min walking distance or time to clinical worsening.

The PACES trial addressed the effects of adding sildenafil to epoprostenol in 267 PAH patients. The most pertinent findings of this study were significant improvements after 12 weeks in 6MW and time to clinical worsening. There are many open questions regarding combination therapy, including the choice of combination agents, the optimal timing [initial combination (in naive patients) or sequential combination (according to the response to the first drug)], when to switch, and when to combine.

Balloon atrial septostomy: Creation of an inter-atrial right-to-left shunt can decompress the right heart chambers, and increase LV preload and CO. In addition, this improves systemic O2 transport despite arterial O2 desaturation and decreases sympathetic hyperactivity. The recommended technique is graded balloon dilation atrial septostomy, which produces equivalent improvements in haemodynamics and symptoms but reduced risk compared with the original blade technique. Patients with advanced right ventricular failure who have not benefited from pharmacologic treatment and who have arterial oxygen saturations within an acceptable range should be considered for percutaneous balloon atrial septostomy.

Failure of pharmacologic treatment in patients with PAH should lead to consideration of lung transplant.

CONCLUSION
Past decade has seen the evolution of PAH from that of a rare and incurable fatal disease to that of a not so uncommonly encountered syndrome that is a component of numerous clinical scenarios and that can be managed effectively to reduce symptoms and prolong life. Advances in understanding the mechanisms, clinical presentations, and natural history of PAH, as well as treatments for patients with PAH, continue to evolve. To promote this progress rely on the prompt recognition and evaluation of suspected PAH cases by physicians and the application of effective treatment and clinical study protocols in dedicated centers.

REFERENCES


