Identifying Appropriate Treatment & Management Strategies in Pulmonary Arterial Hypertension

Harold I. Palevsky, M.D.
Perelman School of Medicine of the University of Pennsylvania
Penn Presbyterian Medical Center
Philadelphia, PA

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Pulmonary Hypertension:
Simply high blood pressure within the pulmonary vascular bed.

Key Issues:
1) Making the correct diagnosis
2) Assessing disease severity
3) Choosing an initial therapy
4) Reassessing the patient and their response to therapy
**Definition of Pulmonary Hypertension (PH)**

Right Heart Catheterization Confirmed

Increased mean pulmonary arterial pressure (mPAP) to >25 mm Hg at rest

(upper limit of normal is age dependent, and is <20 mmHg)

**2009 Clinical Classification of Pulmonary Hypertension: 5 Groups**

- Group 1 – Pulmonary arterial hypertension (PAH)
- Group 2 – Pulmonary hypertension associated with left heart disorders
- Group 3 – Pulmonary hypertension associated with intrinsic lung diseases and/or hypoxemia
- Group 4 – Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group 5 – Pulmonary hypertension due to miscellaneous and/or multifactorial causes
Definition of Pulmonary Arterial Hypertension (PAH)

Right Heart Catheterization Confirmed

Increased mean pulmonary arterial pressure (mPAP)*  >25 mm Hg at rest
Normal pulmonary capillary wedge pressure (PCWP)  <15 mm Hg
Increased pulmonary vascular resistance (PVR)†  >3 Wood units

* Normal resting mPAP = 8 – 20 mm Hg.
† In ACCF/AHA expert consensus; in 4th World Symposium on PH, increased PVR listed without a specific value.


Pulmonary Arterial Hypertension

• Disorders of increased pulmonary vascular resistance (PVR) as a consequence of structural changes to pulmonary arterial bed

• Symptoms/morbidity/mortality are determined by the effects of PVR (RV afterload) on right ventricular function and cardiac output (CO)

• Pulmonary artery pressure is not the disease but
• is a result of the relationship between resistance and flow (P = PVR x CO). At the same PVR, PA pressures will vary depending upon the cardiac output.
2009 Clinical Classification of Pulmonary Hypertension: Group 1
(Pulmonary Arterial Hypertension)

- Idiopathic (IPAH)
- Heritable (HPAH)
  - BMPR2
  - ALK1
  - Endoglin (with or without hereditary hemorrhagic telangiectasia)
  - Unknown
- Drugs and Toxins induced
- Associated with (APAH)
  - Connective Tissue Diseases
  - HIV Infection
  - Portal Hypertension
  - Congenital Heart Diseases
  - Schistosomiasis
  - Chronic Hemolytic Anemias


Association Between Methamphetamine Use and IPAH

Patients Reporting Use (N=340)

Retrospective analysis at single PH center of adults with PH.

2009 Clinical Classification of Pulmonary Hypertension: Group 1’

- Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)


Pulmonary Venous Occlusive Disease / Pulmonary Capillary Hemangiomatosis

- Shares characteristics of IPAH
  - Histology
  - Clinical features
  - Genetic alterations—familial forms for PVOD/PCH (with or without identified mutations)
- Distinct features
  - Crackles and clubbing, ground glass opacities, septal thickening, mediastinal adenopathy, hemosiderin-laden macrophages, lower DLCO and PaO2
  - **Response to therapy is different than IPAH**
    - Risk for pulmonary edema with PAH-specific medications

2009 Clinical Classification of Pulmonary Hypertension: Group 2

- Pulmonary hypertension associated with left heart disease:
  - Systolic dysfunction
  - Diastolic dysfunction
  - Valvular disease


2009 Clinical Classification of Pulmonary Hypertension: Group 3

- Pulmonary hypertension associated with intrinsic lung diseases and/or hypoxia:
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Pulmonary diseases with a mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental abnormalities

2009 Clinical Classification of Pulmonary Hypertension: Group 4

• Chronic thromboembolic pulmonary hypertension (CTEPH)


2009 Clinical Classification of Pulmonary Hypertension: Group 5

Pulmonary hypertension with unclear and/or multifactorial mechanisms:

• Hematologic disorders: myeloproliferative disorders, post-splenectomy state, chronic hemolytic anemias
• Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, vasculidities, lymphangioleioymomatosis, neurofibromatosis
• Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
• Others: obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Progressive Pulmonary Vascular Disease

- Is initially associated only with exercise related symptoms and pulmonary hypertension
- Progresses to resting pulmonary hypertension (maintained cardiac output)
- Limits the ability to increase cardiac output during periods of increased demand
- Eventually limits even resting cardiac output
Hemodynamic Changes Correlate With Disease Progression

PAH is a disease of increased/increasing resistance (PVR)

<table>
<thead>
<tr>
<th>CO</th>
<th>PAP</th>
<th>PVR</th>
<th>RAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presymptomatic/Compensated</td>
<td>Symptomatic/Decompensating</td>
<td>Worsening/Decompensated</td>
<td></td>
</tr>
</tbody>
</table>

Time

PAP=PVR×CO

Symptoms develop and progress as the ability to maintain or increase cardiac output is compromised and the right ventricle progressively fails.

CO=cardiac output; PAP=pulmonary arterial pressure; PVR=pulmonary vascular resistance; RAP=right atrial pressure.

Signs and Symptoms of PAH

– Initial signs and symptoms
  - Dyspnea (on exertion)
  - Fatigue
  - Pre-Syncope
  - Edema
  - Dizziness
  - Angina

– Non-specific nature of complaints can lead to:
  - Confusion with other conditions
  - Delay in establishing a diagnosis
Little Progress in PAH Diagnosis Over The Past 25+ Years

<table>
<thead>
<tr>
<th></th>
<th>NIH-PPH Registry 7/81-9/85</th>
<th>French Registry 10/02-10/03</th>
<th>Reveal Registry 3/06-9/07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>187</td>
<td>674</td>
<td>2525</td>
</tr>
<tr>
<td>Mean time from onset of symptoms to diagnosis of PAH</td>
<td>2.03 years (median- 1.27 years)</td>
<td>2.25 years (median - 1.13 years)</td>
<td>2.84 years</td>
</tr>
<tr>
<td>% patients functional class III or IV at diagnosis</td>
<td>71% (of 121 incident cases)</td>
<td>81%</td>
<td>73.6%</td>
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Evaluation of Suspected Pulmonary Hypertension (I)

History
Physical Examination
Testing
- screening for PH
- confirming the diagnosis of PH
- establishing the etiology of the PH
Evaluation of Suspected Pulmonary Hypertension (II)

Laboratory Studies
– Complete blood count, Coagulation profile,
– Liver function tests, Collagen vascular screen,
– HIV serology

Chest radiograph +/- CT scan (?HRCT, ?CTA)
Electrocardiogram

Pulmonary Function Tests
– Spirometry, Lung volumes, **Diffusing capacity**, Arterial blood gas

Evaluation of Suspected Pulmonary Hypertension (III)

Ventilation-Perfusion Lung Scan
– Pulmonary angiography – if indicated

Echocardiogram (at rest, and/or with exercise)

Exercise test
– (including an assessment for arterial oxygen desaturation during exertion)

Cardiac Catheterization
Sleep study – if indicated
The Most Frequent Initial Symptom of PAH is Dyspnea on Exertion

If symptoms occur during exertion, and the resting evaluation is not informative, we must evaluate the patient during exertion if we are to detect early disease/establish a diagnosis:
- Post-exercise PFTs
- Cardiopulmonary exercise test (CPET)
- Exercise echocardiogram
- Exercise during (right heart) catheterization

Cardiac Catheterization

To exclude congenital heart disease and/or coronary artery disease
To measure pulmonary capillary wedge pressure and/or LVEDP
To establish severity and prognosis of PH/PAH
To test vasodilator (CCB) therapy (if PAH)

*Catheterization is required for almost every patient with suspected pulmonary hypertension*
**ACCP Consensus: Definition of a Vasodilator Responder**

- Decrease in mean PAP by at least 10 mm Hg
- Reduction in PA pressures to an absolute mean PAP <40 mm Hg
- Unchanged or increased CO

It is essential to follow patients treated with CCBs closely to make sure the clinical response is as anticipated, to make sure there are no side effects of therapy, and very importantly, to make sure the response is sustained.

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**Summary: Approach to PAH**

- High index of suspicion
- Thorough diagnostic evaluation
- Exclude thromboembolic disease
- Right heart catheterization is required prior to initiating therapy to confirm the diagnosis of PAH, and to assess prognosis
- Vasodilator testing to eliminate inappropriate CCB use
### Mediators and Pathways in PAH

<table>
<thead>
<tr>
<th>Increased Activity</th>
<th>Reduced Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin-1</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Prostacyclin synthase</td>
</tr>
<tr>
<td>Thromboxane A₂</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>Clotting Factors</td>
<td>Nitric oxide synthase</td>
</tr>
<tr>
<td>Angiopoietin-1</td>
<td>VIP</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Kᵥ channel</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Fibrinolysis</td>
</tr>
<tr>
<td>Oxidant stress</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
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</tbody>
</table>

PAI=plasminogen activator inhibitor; VIP=vasoactive intestinal peptide.
Pathophysiology of PAH: An Integrated View

Genetic Predisposition → Proliferation
Risk Factors And Triggers
Altered Pathways and Mediators
Vascular Remodeling

- Vasoconstriction
- Thrombosis

Targets for Current Therapies in PAH

Prostacyclin Pathway
- Arachidonic Acid
- Prostacyclin Synthase
- Prostacyclin
- cAMP
- Prostacyclin Derivatives
- Vasodilation and Antiproliferation

Endothelin Pathway
- Big Endothelin
- Endothelin-converting Enzyme
- Endothelin-1
- Endothelin Receptor Antagonists
- Endothelin Receptor A
- Endothelin Receptor B
- Vasoconstriction and Proliferation

Nitric Oxide Pathway
- L-Arginine
- Nitric Oxide Synthase
- Nitric Oxide
- cGMP
- Exogenous Nitric Oxide
- Phosphodiesterase Type-5
- Phosphodiesterase Type-5 Inhibitors
- Vasodilation and Antiproliferation
### Current Treatment Options Specifically FDA Approved for PAH (as of 4/13)

- **Prostacyclin (PGI₂) analogues**
  - Continuous IV Infusion Epoprostenol (Flolan, generic epo)
  - Continuous IV Infusion Thermostable Epoprostenol (Veletri)
  - Continuous SC or IV Infusion Treprostinil (Remodulin)
  - Inhaled Iloprost (Ventavis)
  - Inhaled Treprostinil (Tyvaso)
- **Endothelin receptor antagonists (ETRA)**
  - Oral Bosentan (Tracleer)
  - Oral Ambrisentan (Letairis)
- **Phosphodiesterase type 5 inhibitors (PDE-5i)**
  - Oral or IV Sildenafil (Revatio, generic sildenafil)
  - Oral Tadalafil (Adcirca)

### Goals of Management of PAH

- Improve survival
- Prevent worsening
- Improve hemodynamics
- Improve exercise capacity
- Maintain or improve functional class
- Improve daily functioning and quality of life
In PAH – the major determinants of symptoms, of the risk of progression and of survival are markers of Right Ventricular Function (and are not the pulmonary arterial pressures)

**PAH Determinants of Risk (ACCF/AHA)**

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Determinants of Risk</th>
<th>Higher Risk</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6MW distance</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Peak VO₂ &gt;10.4 mL/kg/min</td>
<td>CPET</td>
<td>Peak VO₂ &lt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiographic findings</td>
<td>Pericardial effusion, significant RV dysfunction, RA enlargement</td>
</tr>
<tr>
<td>RAP &lt;10 mm Hg, CI &gt;2.5 L/min/m²</td>
<td>Hemodynamics</td>
<td>RAP &gt;20 mm Hg, CI &lt;2.0 L/min/m²</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

RV=right ventricle/ventricular; WHO=World Health Organization; 6MW=6-minute walk; VO₂=maximal oxygen consumption; CPET=cardiopulmonary exercise testing; RA=right atrium/atrial; RAP=right atrial pressure; CI=cardiac index; BNP=brain natriuretic peptide. McLaughlin VV et al. J Am Coll Cardiol. 2009;53:1573-1619.
General Medical Management of PAH

Oxygen (at rest, with exertion, at night)
Warfarin (if not otherwise contraindicated)
Diuretics (especially aldactone)
Digoxin (if RV dilated and/or depressed)
Lifestyle adjustments
- Avoidance of stimulants and decongestants
- Low-salt diet; possibly fluid restriction
- Regular exercise
- Stress reduction
- Avoidance of pregnancy

Rational for Anticoagulation in Pulmonary Hypertension

- High prevalence of microthrombotic lesions in histologic studies (in situ thrombosis / eccentric intimal proliferation) – seen in all etiologies of pulmonary hypertension
- High risk for venous thromboembolic disease
- Beneficial effect on survival (Multiple studies in PAH (predominately iPAH); all using warfarin anticoagulation)
- Theoretic beneficial effect on pulmonary vascular remodeling (unfractionated heparin)
Eccentric Intimal Proliferation/In situ Thrombosis

Exercise training significantly improves six-min walk distance in PAH

When to Initiate PAH-specific Therapy

• No data support a “wait-and-see” approach to treating diagnosed PAH
• Data suggests that patients assigned to placebo in randomized controlled trials may fail to “catch-up” when enrolled into long-term observational arms
• In FC II patients, bosentan (EARLY Trial) improved outcomes consistent with usefulness of early intervention


Considerations for Selecting Initial Therapy for PAH

• Severity of symptoms
• Rate of progression
• Physical examination (right-heart failure)
• Echocardiogram (RV size and function)
• 6-minute walk distance
• BNP/NT-proBNP
• Capability of patient to manage inhaled or parenteral therapy (Parenteral therapy is first choice therapy in rapidly progressing and advanced disease (Class IV))
• Other issues: Drug-drug interactions, adverse events, comorbid conditions (eg, diabetes), route of administration, dosing, cost
2009 Guidelines: Use of PAH-Specific Therapies Available in the US

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>WHO Class II</th>
<th>WHO Class III</th>
<th>WHO Class IV</th>
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<tbody>
<tr>
<td>A</td>
<td>Ambrisentan, bosentan, sildenafil</td>
<td>Ambrisentan, bosentan, epoprostenol IV, iloprost inh, sildenafil</td>
<td>Epoprostenol IV</td>
</tr>
<tr>
<td>B</td>
<td>Tadalafil</td>
<td>Tadalafil, treprostinil SC</td>
<td>Iloprost inh</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>Treprostinil SC</td>
</tr>
<tr>
<td>E/B</td>
<td>Treprostinil IV</td>
<td>Treprostinil IV, initial combo tx</td>
<td></td>
</tr>
<tr>
<td>E/C</td>
<td></td>
<td>Ambrisentan, bosentan, sildenafil, tadalafil</td>
<td></td>
</tr>
<tr>
<td>Approved in 2009</td>
<td>Treprostinil inh*</td>
<td>Treprostinil inh*</td>
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</table>

*Approved after guidelines published.

Modified from the ACCF/AHA Consensus PAH Treatment Algorithm (2009)

Anticoagulate ± Diuretics ± Oxygen ± Digoxin → Acute Vasoreactivity Testing (not performed in patients with right heart failure)

Positive

Less Severely III

ERAs or PDE-5 is (oral)

Iloprost or Treprostinil (inhaled)

More Advanced Disease

Epoprostenol or Treprostinil (IV)

Iloprost or Treprostinil (inhaled)

Treprostinil (SC)

Negative

More Advanced Disease

No

Sustained Response

Oral CCB

Less Severely III

ERAs or PDE-5 is (oral)

Iloprost or Treprostinil (inhaled)

Positive

Less Severely III

ERAs or PDE-5 is (oral)

Iloprost or Treprostinil (inhaled)

Reassess: consider combination therapy

Investigational Protocols

Yes

Continue CCB

Investigational Protocols

Atrial septostomy

Lung transplantation

REVEAL Database: Overall PAH-specific therapy at time of enrollment
(first 2439 patients enrolled into the REVEAL Registry)

No therapy: 266 patients
1 Agent: 1164 patients
2 Agents: 819 patients
3 Agents: 190 patients

N=2438.


PAH: What Should our Goals Be?

- Reversal of vascular injury
- Improvement in RV function
- Improvement in QOL and survival
- Normalization of pulmonary pressures
Short-term studies may not accurately predict long-term response

How do we tell when a patient is in need of escalation of therapy?

- Failure to improve on monotherapy
- Improved, but not to the satisfaction of patient and/or physician (by objective end points, symptoms, QOL, etc.)
- Improved for a period of time, but now deteriorating
Monitoring a patient over time to assess for response to therapy vs. need for escalation of therapy?

- Office visits – for exams, evaluation of symptoms and QOL assessments
- Lab monitoring (BNP/NT-proBNP)
- Functional assessments (i.e. 6 MWD, exercise testing)
- Echocardiograms – for assessment of chamber sizes, RV function, pericardial effusions, etc.
- Repeat right heart catheterizations (when indicated)

?Why Initiate Combination Therapy?

- To target multiple pathogenic pathways, thereby achieving synergistic effects
- To potentially allow dose reduction of one or more of the therapies, thereby reducing the toxicities of full dose mono-therapy
- Combination therapy is the standard of care in most chronic medical conditions (i.e. CHF, DM systemic hypertension, COPD, etc.)
Goal-oriented Therapy

Diagnosis of PAH
Vasoreactivity test negative
NYHA III or IV

Baseline examination and 2 to 6 monthly re-evaluation to assess treatment goals
6-MWD >380 m, peak VO₂ >10.4 ml/min/kg, peak SBP >120 mmHg during exercise

Treatment goals not met
- First-line treatment bosentan
- Addition of sildenafil
- Addition of inhaled iloprost
- Transition from inhaled to intravenous iloprost
- Highly urgent lung transplantation

Treatment goals met
- Treatment continued

Hoeper MM et al. *Eur Respir J.* 2005; 26:858-863

K-M Estimates of Survival with Combination Therapy

Cumulative survival (IPAH)

Treatment vs historical control group, \(P=0.011\)
Treatment vs expected survival, \(P<0.001\) for all time points

Subjects at risk \(n\)

0.0 0.2 0.4 0.6 0.8 1.0

Time (months)

0 6 12 18 24 30 36

First-line bosentan
Addition of sildenafil/iloprost
2002-2004

Historical control group
1999-2001

Expected survival (NIH)

How to initiate initial PAH therapy: Up-front combination Rx, or Add-on?

- A cancer chemotherapy type model?
  - At diagnosis in patients with severe limitations/severe disease/rapid course (or potentially all patients)?

- A CHF or systemic HTN type model?
  - In patients who do not hit treatment targets after a period of mono-therapy (i.e. goal directed therapy)?
  - Or with clinical decline/deterioration?

Summary

- Early and accurate diagnosis is crucial.
- Once a diagnosis is established, therapy should be instituted. The initial therapeutic choice(s) depends upon the patient's diagnosis, clinical co-morbidities, clinical circumstance, and their functional status. Treatment must be individualized!
- Ongoing reassessment of the patient's clinical status and response to therapy is mandatory.
- If the patient does not meet treatment goals, then switching to an alternative agent, or adding a second (or perhaps a third agent) may be appropriate; considering lung transplantation (referral) may also be warranted.
- Referral to an experienced PH Center should be considered for all patients, and may be necessary for parenteral therapies, and consideration of clinical trials and investigational agents