Pulmonary Hypertension for the Primary Care Provider

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Disclosures: (no direct honorariums; research meetings support)
- Research PI: Actelion, United Therapeutics.

Objectives:
- Review the DEFINITION of pulmonary hypertension (PH)
- Discuss the different GROUPS of PH Patients
- Examine the PROGNOSIS of PH patients in the different GROUPS
- Differentiate the BENEFITS and SIDE EFFECTS of different treatments for PH patients.
- Review new guidelines for assessment of ADEQUATE TREATMENT RESPONSE in PAH.

Introduction to Pulmonary Hypertension:

Pulmonary Hypertension Comes in Several Varieties:

- PH with Lung Disease and/or Low Oxygen Levels
- PH with Left Heart Disease
- Chronic Thrombosis (clot) PH
- Miscellaneous

Normal Pulmonary Artery (PA) Pressure: 30/15, mean 20 mmHg.

Pulmonary Hypertension (PH) when mean > 25 mmHg (40/20 mmHg) and Elevated Pulmonary Vascular Resistance (PVR)

Introductory Questions:
- Is Pulmonary HTN common?
- If so, Which Group?
- Is Pulmonary HTN rare, an "orphan" disease?
- If yes, which Group?
- Can Pulmonary HTN be cured?
- Are there effective treatments?
- Yes, Many patients with left sided heart failure have Group II Pulmonary HTN.
- Yes, Group I PAH. Pulmonary HTN remains an uncommon disease.
- Chronic PE patients who have a successful surgery return to near normal.
- OSA patients on CPAP.
- Yes, particularly for Group I PAH patients now.
1. Epidemiology of PH by Echo
   - Single echo lab / Australian community of 165,450
   - Etiology of PH noted on echocardiogram

2. Right Heart Catheterization: The Definitive Diagnosis:
   - Normal Pulmonary Artery (PA) Pressure: 30/15, mean 20 mmHg.
   - Pulmonary Hypertension (PH) when mean > 25 mmHg (40/20 mmHg and Elevated Pulmonary Vascular Resistance (PVR))

3. Miscellaneous, 2.7%
   - Lung disease, Sleep-related hypoventilation, 9.3%
   - Miscellaneous, 2.7%

4. Pulmonary Hemodynamics: Pre-capillary and Post-capillary Patterns

5. 5th World Symposium on PH: Classification /GROUPS
   - Pulmonary arterial hypertension
   - Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   - Persistent PH of the newborn
   - Pulmonary hypertension due to left heart disease
   - Pulmonary hypertension due to lung diseases and/or hypoxia
   - Chronic thromboembolic PH (CTEPH)
   - PH with unclear multifactorial mechanisms

6. Is There a Reason to Suspect PH? Clinical Presentation
   - History:
     - Dyspnea (60%)
     - Fatigue (27%)
     - Chest pain (22%)
     - Edema (22%)
     - Syncope (17%)
     - Dizziness (10%)
     - Cough (14%)
     - Palpitations (13%)
   - Diagnostic Tests:
     - H & P, CXR, ECG: Suspicion, Risk Factors
     - PFT, ABG, Overnight Sleep study
     - VQ scan best screening test for Chronic PE. CT Angio complementary tests.
     - Echo: Structure, function, ESTIMATE hemodynamics
     - Exercise Testing: CPET, 6MW
     - Heart Catheterization
Pulmonary Hypertension Risk Factor List:
- Cardiovascular Disease
- Lung Disease
- Sleep History
- Thyroid Disease: autoimmune
- Liver disease
- Collagen vascular disease
- Blood, clotting disorders, splenectomy
- Viral Exposure Risk: HIV, Hepatitis.
- Recreational Drug Use: Cocaine, Meth, other amphetamines.
- Diet Pill, Weight loss prescription:

Is There a Reason to Suspect PAH?
Echo
- RV enlargement
- RA enlargement
- Septal straightening
- Loss of IVC inspiratory collapse
- Tricuspid regurgitation
- Pericardial effusion
- Decreased RV systolic dysfunction
  - TAPSE (tricuspid annular plane systolic excursion)

Estimation of RV Systolic Pressure (RVSP)

\[ \text{RVSP} = 4(\text{velocity of TR})^2 + \text{RA pressure} \]
\[ = 4(4)^2 + 20 \]
\[ = \sim 84 \text{ mm Hg} \]

Peak tricuspid regurgitation velocity (m/s) | Presence of other echo PEEP signs | Echocardiographic probability of pulmonary hypertension
---|---|---
<2.8 or not measurable | No | Low
<2.8 or not measurable | PA 30 | Intermediate
2.9–3.4 | PA 35–45 | No
2.7–2.4 | PA > 45 | Yes
>3.4 | PA > 45 | Not required

PA = Estimated PA systolic pressure.

Echocardiogram prediction of PH: ERS 2015

Case: TN
- 60 yo female
- Alcohol Abuse, Osteopenia
- Fall and Pelvic fracture with severe left femur fracture.
- Pre-op evaluation done.
- Referred 2013 for evaluation of abnormal echo with RV enlargement and PH suggested by echo.
- Normal VQ scan, US no cirrhosis.
- Mild elevation in ANA.
Mild PAH20.avi
Mild PAH56.avi
Diastole in short-axis view
Systole in short-axis view
TR jet
Apical 4-chamber view

PH Case -DS

- 60 year old manager
- DOE for months: Stairs at work and Lawn work now more difficult. WHO functional class?
- PMH: Viral CM; ? HTN on ARB
- FH: Estranged sister with lung condition; on pump medication, oxygen and now pills
- SH: Manager, Layoffs coming, Insurance?
- Exam: JVP 4 cm, Loud P2, TR Murmur, RV impulse, no edema.
- Walk test: 440 m
- VQ scan: Normal
- ECG: NSR, R axis, RVH

Case DS

PH Echocardiogram on 03/06/07:
- Left ventricular EF 40-45%. Mild diastolic dysfunction was identified. Left atrium appears visually normal (adjusted for BSA 17ml/M2).
- Right ventricle is severely enlarged and has severe systolic dysfunction.
- Estimated PASP: at least 65 mm Hg. IVC compatible with RAP of 10 mm HG. Agitated saline contrast at rest with Valsalva reveals no shunt.
- No pericardial effusion is seen.

Case DS

What Diagnoses need to be considered?
What additional tests do you want?
Outside Echo suggests pulmonary hypertension with RV dysfunction.

Case DS

Right heart catheterization on 04/16/07 at FMLH:
- RA Press 7;
- RV Press 93/13;
- PA Press 94/40/mean 62;
- PWP Wedge Pressure 12, LV EDP: 10
- Cardiac Output CO / Index CI: 3.9 lpm/1.95 lpm/m2; HR:65/min; PVR: 12.2 WU; Mixed Venous Sat% 62%.
- Vasodilator trial with Nitric Oxide (10 ppm) revealed: No significant change.
- Severe Precapillary Pulmonary HTN. Normal LV filling pressures.

Case TN (2)

- Right Heart Catheterization done: RA pressure 4, PA pressure mean 26, PAWP 9 (all mm Hg). CI 2.8 l/min m2.
- Mild PAH, Idiopathic with preserved RV function.
- Recommended to complete surgery and then return promptly for treatment. LOW RISK Status to start.
- Surgery Successful with no complications.
- Lost to fu for period of time.
Case DS

- What Diagnoses to be considered?
- **Group I PAH.** Heritable PAH, Idiopathic PAH
- Are there any barriers to treatment? Insurance.

Group I PAH: Pulmonary Arterial Hypertension:

- Symptoms often nonspecific; average 14-month delay from initial presentation to diagnosis
- Poor prognosis without therapy and close follow-up
- Evaluation must be methodical and include right heart catheterization (RHC)
- Prognosis improves with therapy, but PAH remains a progressive fatal disease
- Therapies and management strategies continue to evolve

Idiopathic PAH: Survival

- Incidence: 2-4 cases per million in US
- Poor prognosis in an era lacking therapy 50%-3 year survival
- Therapeutic options and research efforts now offer more HOPE!

5th World Symposium on PH: Classification

<table>
<thead>
<tr>
<th>1. Idiopathic PAH</th>
<th>1. Pulmonary hypertension due to left heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. PAH due to left heart disease</td>
<td>2. IPH due to left heart disease</td>
</tr>
<tr>
<td>3. PAH associated with connective tissue disease</td>
<td>3. PAH due to left heart disease</td>
</tr>
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Most Common Cause of Elevated PAPs by Echo: Left Heart Disease

**Symptoms**
- paroxysmal nocturnal dyspnea
- orthopnea

**History**
- diabetes
- hypertension
- obesity
- coronary artery disease
- metabolic syndrome

**ECG**
- atrial fibrillation
- absence of right axis deviation

**Echo**
- left atrial enlargement
- left ventricular hypertrophy
- normal RA, RV
- abnormal diastolic filling
- mitral or aortic disease

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Pulmonary Venous Hypertension/ Left Heart Disease: A Simplified View

- Normal, or mildly elevated transpulmonary gradient with readily apparent cause
  - treat underlying cause
- Substantially elevated transpulmonary gradient (PH out of proportion to LHD)
  - treat cardiovascular risk factors (including aggressive volume control) as best you can
  - improvement in PH may be slow (months)
  - No FDA-approved therapies for diastolic dysfunction yet

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5th World Symposium on PH: Classification

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<th>Pulmonary arterial hypertension</th>
<th>3. PH due to lung disease and/or hypoxia</th>
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<td>Pulmonary veno-occlusive disease</td>
<td>3.1 Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Pulmonary capillary hemangiomatosis</td>
<td>3.2 Hypersensitivity pneumonitis with nodal restriction and/or pleural plaques</td>
</tr>
<tr>
<td>Persistent PH of the newborn</td>
<td>3.3 Pulmonary hypertension due to left heart disease (with or without pulmonary hypertension)</td>
</tr>
<tr>
<td>Pulmonary venous obstruction</td>
<td>3.4 Pulmonary hypertension due to left heart disease (without pulmonary hypertension)</td>
</tr>
</tbody>
</table>

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Sleep-disordered Breathing and PH

- Nocturnal hypoxemia results in pulmonary arterial constriction and remodeling
- PH can occur with either obstructive sleep apnea (OSA) or central sleep apnea
- PH can occur with obstructive sleep apnea in the absence of intrinsic heart or lung disease
- Little correlation in severity of OSA and degree of PH:
  - PH is usually Mild; Mean <35 mmHg

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Pulmonary Hypertension in Lung/Respiratory Disease

- May explain worsening symptoms in patient with stable PFTs
- May contribute to exercise limitation: ventilatory vs cardiovascular limitation
- Disproportionately low DLCO may suggest pulmonary vascular disease
- Correlates better with low oxygen levels vs PFTs
- NO approved PH therapies. Positive Small studies or case series. (BUT negative trials)

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PH as a Predictor of Survival in Patients With IPF

- N=79
- No difference in lung volumes lower 6MWD
- PH (mPAP >25 mm Hg)
- p<0.001

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5th World Symposium on PH: Classification

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
     1.2.1 BMPR2
     1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
     1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
     1.4.1 Connective tissue disease
     1.4.2 HIV infection
     1.4.3 Portal hypertension
     1.4.4 Congenital heart diseases (update)
     1.4.5 Schistosomiasis
   1’. Pulmonary veno-occlusive disease
   and/or pulmonary capillary hemangiomatosis
   1’’. Persistent PH of the newborn

2. PH due to left heart disease
   2.1 LV systolic dysfunction
   2.2 LV diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. PH due to lung diseases and/or hypoxia
   3.1 COPD
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases (update)

4. Chronic thromboembolic PH

5. PH with unclear multifactorial mechanisms
   5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH


Incidence of CTEPH

- Approximately 3% to 4%
- 1-2 yr after acute PE (large, Recurrent higher risk)
- USA: 600,000 cases of acute PE each year
- Only 40% to 50% of CTEPH patients have a history of previous episodes of acute PE
- VQ scan identifies old PE better than CTA


PH Treatment Goals

- Fewer/less severe symptoms
- Improved exercise capacity
- Improved “hemodynamics”
- Prevention of clinical worsening (heart failure, admissions, increased SOB)
- Improved quality of life (benefits versus side effects)
- Improved survival? Achieve “Low Risk” Status

Chronic Adjuvant Therapies in PAH

Oxygen
- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation >90%
- May not correct hypoxia with shunt


Diuretics
- Needed by most patients; hypotension not a contraindication in RV failure (may need BP support)

Anticoagulation
- Recommended in IPAH
- Observational studies only (2 retrospective, 2 prospective); need to balance unproven benefits with known risks
- INR 1.5 – 2.5

Selection of Appropriate Therapy:

GROUP I PAH Patients:

Chronology:
1980s: Calcium Channel Blockers, Diuretics, Oxygen.
1996: IV Epoprostenol (Flolan) - "TPH" only; then 1998 All Group I PAH.
2001: Bosentan (Endothelin Receptor Antag.), first oral drug. Group I PAH.
2003: Sildenafil (PDE5 Inhibitors). Group I PAH.
2013: Riociguat (sGCynlylate Cyclase, CMF) Group I PAH, Group IV PAH.
2019: 12 Drugs: Group I PAH,
Group IV CTEPH. 1 Drug: Riociguat.

(No Approved Drugs: Group II PH - Heart Disease; Group III PH - Lung Disease)

Mechanisms of Action of Approved Therapies for GROUP I PAH (not other groups)

Evolution From Exercise Capacity to Morbidity and Mortality Randomized Controlled Trials

PAH Determinants of Risk

5th World Symposium on PH: Treatment Algorithm

ERS Risk Assessment 2015
Case DS

- What Diagnoses to be considered?
- Group I PAH. Heritable PAH, Idiopathic PAH

Group I PAH.
- High because: Low normal Cardiac Output. High BNP
- Low because: normal RA pressure, Functional class II symptoms, no heart failure.

"INTERMEDIATE RISK"
- Are there any barriers to treatment? Insurance.

PH Case DS

- Treated with Sildenafil alone with improvement; Escalated dose to 80 mg TID
- Walk Test 660 m, no desat
- WHO functional Class I most days. II on some chore days.
- BNP 12
- Echo: Severe RV enlargement; Low normal TAPSE.
- Right Heart Cath 11/08 on Revatio 80 TID.
- RA 7, PA 91/33 mean 55, PWP 8, CO 5.4 CI 2.7 PVR 8.6, MVO2 sat 71, AV02 diff 5.0

New Medication to discuss?

- Approved Therapeutic Targets

- PDE-5 Inhibitor: Sildenafil, Tadalafil Side Effects
  - Nose bleed
  - Headache
  - Dyspepsia
  - Flushing
  - Diarrhea
  - Visual changes
  - Contraindicated with use of nitrates

- sGC Stimulator: Riociguat Side Effects
  - Headache
  - Dizziness
  - Dyspepsia/gastritis
  - Nausea
  - Diarrhea
  - Hypotension
  - Vomiting
  - Anemia
  - Gastroesophageal reflux
  - Constipation
  - Contraindicated in pregnancy, with use of nitrates or NO donors in any form, or with use of PDE inhibitors
Mechanisms of Action of Approved Therapies for
GROUP I PAH (not other groups)

![Mechanisms of Action of Approved Therapies for GROUP I PAH (not other groups)](https://example.com/machanisms.png)

**AMBITION: Effect of Ambrisentan Plus Tadalafil Versus Monotherapy on Clinical Worsening**

- **Combination therapy**
- **Pooled monotherapy**

<table>
<thead>
<tr>
<th>No. at risk:</th>
<th>Combination therapy</th>
<th>Pooled monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>253</td>
<td>131</td>
</tr>
<tr>
<td>Placebo</td>
<td>228</td>
<td>115</td>
</tr>
<tr>
<td>Hazard ratio, 0.50 (95% CI, 0.35-0.72)</td>
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<tr>
<td>p&lt;0.001</td>
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*Death, hospitalization for worsening PAH, disease progression, unsatisfactory long-term clinical response.*

**SERAPHIN: Effect of Macitentan on Disease Progression**

- **Macitentan 10 mg qd**
- **Macitentan 3 mg qd**
- **Placebo**

<table>
<thead>
<tr>
<th>No. at risk:</th>
<th>Macitentan 10 mg qd</th>
<th>Macitentan 3 mg qd</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Patients with no event related to PAH or death from PAH during therapy</td>
<td>250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>6, 12, 18 months</td>
<td>180</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>24, 36 months</td>
<td>135</td>
<td>135</td>
<td>135</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.60 (95% CI, 0.43-0.83)</td>
<td>0.80 (95% CI, 0.55-1.16)</td>
<td>0.70 (95% CI, 0.50-1.00)</td>
</tr>
<tr>
<td>p&lt;0.001</td>
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**Prostacyclin Analogues: Intravenous, Subcutaneous, Inhaled, or Oral**

- **Epoprostenol (Flolan®)**
- **Treprostinil (Remodulin®)**
- **Selexipag (Upral®)**
- **Iloprost (Ventavis®)**

**Endothelin Receptor Antagonists: (Bosentan, Ambrisentan, Macitentan) Side Effects:**

- **Nasal congestion**
- **Abnormal hepatic function**
  - monthly LFTs required for bosentan
- **Anemia**
  - monitor CBC quarterly
- **Edema**
  - lower extremity edema may require diuretic adjustment
- **Teratogenic**
  - Avoid pregnancy.

*PHA Scientific Leadership Council recommends LFT testing at onset of all treatments for PAH and periodically thereafter, at prescriber’s discretion.*

Oral Prostacyclin Therapy: Time to First Morbidity or Mortality Event—GRIPHON

Prostanoid Side Effects

PH Case DS
- Treated with Sildenafil alone with improvement; Escalated dose to 80 mg TID
- Walk Test 660 m, no desat
- WHO functional Class I most days.
- BNP 12
- Echo: Severe RV enlargement; Low normal TAPSE.
- Right Heart Cath 11/08 on Revatio 80 TID.
- RA 7, PA 91/33 mean 55, PWP 8, CO5.4 CI 2.7 PVR 8.6, MVO2 sat 71, AV O2 diff 5.0
- New Medication to discuss?
- Macitentan added to Sildenafil in 2016.
- Doing Great 12 years later - 2019.

Case TN (3)
- Returned : Primary Care MD
- Sildenafil TID monotherapy for PAH in 2014.
- Erratic FU but compensated initially on therapy and better exercise tolerance: ETOH use.
- Returned one year later 2015: Increased edema, DOE, consistent with early RV failure.
- Unable to get in for repeat Right Heart Catheterization.
- Diuretics added to Sildenafil.
- echo shows worsening RV size and Worsening function. Estimated PASP is > 60 mmHg. Estimated RA pressure is higher
- Not candidate for infusion therapy. Social barriers
- Palliative care 2018.

Summary
- PH should be in the differential diagnoses for the dyspneic patient.
- Usual diagnostic studies can determine who has a higher likelihood of PH and help to determine the possible cause and Group.
- Therapy follows according to the Group.
- Group I PAH-specific therapies promote vasodilation and remodeling, leading to improved RV function and exercise.
- Selection of initial therapy largely depends upon severity of disease at diagnosis
  - low-risk patients can be treated with oral agents
  - Initial or early combination therapy of benefit
  - high-risk patients require parenteral prostacyclins

Summary—Cont’d
- Longitudinal assessment of PAH patients includes monitoring of:
  - clinical parameters
  - functional parameters
  - hemodynamic parameters
  - laboratory parameters
  - imaging parameters
- Current strategy is to achieve “Low Risk” Status in all patients. Directed combination therapy and potent therapies should be used in a timely fashion to achieve this status.
Correct Diagnosis, Best Plan, Partner before you jump in......

PH Patient Chronic Care Needs:
Heart Failure Overlap (Group II),
Chronic Lung Disease Overlap (Group III),
Specialty PH Care (Groups I, IV, V)

MCW-FMLH: Among first 26 PHA CC Centers in USA

Pulmonary Hypertension Program physicians and staff

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