Pulmonary Arterial Hypertension: Evaluation and Treatment

Consensus Guidelines

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Disclosures

- Employee - American College of Physicians and *Annals of Internal Medicine*
- Research grant to the University of Pennsylvania - Actelion for REVEAL
- Chair - ACCP Guideline in PAH
Normal Pulmonary Vasculature

A LOW RESISTANCE SYSTEM
Hemodynamic Definition of PH/PAH

**PH**
Mean PAP ≥25 mm Hg

**PAH**
Mean PAP ≥25 mm Hg *plus*
PCWP/LVEDP ≤15 mm Hg

ACCF/AHA CECD includes PVR >3 Wood Units

Progression of PAH

Pre-symptomatic/Compensated

Declining/Decompensated

Right Heart Dysfunction

Mandel and Taichman, 2006
Idiopathic PAH (PPH) Survival

NIH Registry

 Median 2.8 years

Advanced Disease at Diagnosis

Class I - 4.9 years
Class IV – 0.5 years

Symptoms of PAH

Dyspnea – 84%
Fatigue – 29%
Angina – 20%
Edema – 20%
Dizziness – 14%
Syncope – 20%

→ Delayed Diagnosis
Most PH is not PAH
## Classification - PH

1. PAH

2. Left Heart Disease

3. Hypoxemic Lung Disease

4. Thromboembolism (CTEPH)

5. Other: Heme / Onc

---

Classification - PH

1. PAH

2. Left Heart Disease
   Systolic, Diastolic, Valvular

3. Hypoxemic Lung Disease

4. Thromboembolism (CTEPH)

5. Other: Heme / Onc

Classification - PH

1. PAH
2. Left Heart Disease
3. Hypoxemic Lung Disease
   COPD, ILD, Sleep Apnea, Deformity, Altitude
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Classification - PH

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   COPD, ILD, Sleep Apnea, Deformity, Altitude
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1. PAH
   - Idiopathic (IPAH)
   - Heritable (HPAH)
   - Drugs and Toxins
   - Connective Tissue Diseases
   - HIV Infection
   - Portal Hypertension
   - Congenital Heart Diseases
   - Schistosomiasis
   - Chronic hemolytic anemia
   - PPHN
   - PVOD, PCH

2. Left Heart Disease

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Diagnosis Drives Therapy

1. PAH
2. Left Heart Disease
3. Hypoxemic Lung Disease
4. Thromboembolism (CTEPH)
5. Other: Heme / Onc
1. PAH

+ Efficacy / Approved Rx:

- Prostenoids
- Endothelin Antagonists
- PDE5 Inhibitors
Diagnosis Drives Therapy

- No Efficacy
- Suggests Harm

**Prostenoids**

**Endothelin Antagonists**

**PDE5 Inhibitors:**

2. Left Heart Disease

3. Hypoxemic Lung Disease

4. Thromboembolism

5. Other: Heme / Onc
Diagnosis Drives Therapy

Suspect PAH

Evaluate PH

Confirm
Classify
Severity

Treat
Diagnosis Drives Therapy

Suspect PAH

- Dyspnea
- Fatigue
- Chest pain
- Edema
- Syncope
- Dizziness
- Cough
- Palpitations

- Family history
- Connective tissue disease
- Congenital heart disease
- Portal hypertension—OLT candidate
- Environmental/drug factors
- HIV
- *Not responding to Rx (e.g., asthma)*

Diagnosis Drives Therapy

Suspect PAH

- JVD
- RV S3
- Hepatomegaly
- Edema
- Ascites
- Low BP, low PP, cool extremities

Diagnosis Drives Therapy

Suspect PAH

Evaluate PH

Confirm
Classify
Severity

Treat
Echocardiogram

Normal

Severe RH Failure

Image courtesy of Vallerie McLaughlin, MD
Echocardiogram

Suggests PH - NOT PAH

STOP
Classification - PH

1. PAH
2. Left Heart Disease
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PH?

2. Left Heart Disease

- Echocardiogram
- LFTs and clinical evidence of cirrhosis and portal htn

Exam

- CXR
- ECG

PFTs

Sleep study

Ventilation-perfusion scan, Contrast CT, Angiography

3. Hypoxemic Lung Disease

- HIV test
- Autoantibody tests

4. CTEPH

- Functional test
  - BNP
  - RH cath
  - Vasodilator test
Is There a Reason to Suspect PAH? CXR

- Normal
- Abnormal
  - Peripheral hypo-vascularity (pruning)
  - Prominent central pulmonary artery
  - RV enlargement into retrosternal clear space

Is There a Reason to Suspect PAH? ECG

Right Axis

RVH

RV Strain

Right Atrial Enlargement
Possible PH

NOT PAH

Diagnosis drives therapy
Ventilation Perfusion Lung Scan

CTEPH

IPAH
CTEPH- “Curable” PH- Not to Be Missed

Diagnosis Drives Therapy
Diagnosis Drives Therapy

Suspect PAH

Evaluate PH

Confirm
Classify
Severity

Treat
Cardiac Cath in PH

- **Confirm PH is present**

- **Elucidate cause**
  - Congenital heart disease ("sat run")
  - L heart disease
  - High output
  - Elevated PVR

- **Guide therapy (vasodilator trial)**
PH by Echo ≠ PAH Necessarily

- 374 lung txp pts
- Echo 24–48 h prior to RHC
- Prevalence of PH: 25%

![Bar chart showing overestimation, accurate, and underestimation of PH (-) in studies.](image-url)
Cardiac Cath in PH

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Diagnosis Drives Therapy
Echocardiogram

Suggests PH - NOT PAH

All Guidelines:
R Heart Cath REQUIRED to diagnose PAH
Final Diagnoses - PH Specialty Clinic

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD</td>
<td>5.0%</td>
</tr>
<tr>
<td>VTE</td>
<td>5.0%</td>
</tr>
<tr>
<td>Other</td>
<td>12.0%</td>
</tr>
<tr>
<td>Structural Ht Dz</td>
<td>13.0%</td>
</tr>
<tr>
<td>OSA</td>
<td>19%</td>
</tr>
<tr>
<td>LV Dysfunction</td>
<td>22.0%</td>
</tr>
<tr>
<td>Obstructive Lung</td>
<td>24.0%</td>
</tr>
<tr>
<td>Combined – NON PAH</td>
<td>85.0%</td>
</tr>
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Cardiac Cath in PH

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High-Dose CCBs in IPAH

Survival

% Survival

0 12 24 36 48 60 Months

94%

NR ← 38%

UIC NIH

“Vasodilator Response”

- Fall in mPAP ≥10 mm Hg
- + PAPm (absolute) <40 mm Hg
- + Normal CO

- Effects highly variable, unpredictable, → deaths reported

- CCBs should NOT be used empirically

Diagnosis Drives Therapy

Suspect PAH

Evaluate PH

Confirm
Classify
Severity

Treat
What Is the Optimal Treatment Strategy?

- Anticoagulate ± Diuretics ± Oxygen ± Digoxin

- Acute Vasoreactivity Testing
  - Positive
    - Oral CCB
      - Sustained Response
        - Yes: Continue CCB
        - No: PAH Specific Therapies
  - Negative: PAH Specific Therapies

Supportive Therapies in PAH

- **Diuretics**
  
  Most need; hypotension not absolute contraindication

- **Digoxin**
  
  No long-term data; balance unproven benefits with known risks

- **Oxygen**
  
  Consider exercise, sleep, altitude, aim saturation >90%

- **Anticoagulation**
  
  Recommended in IPAH
  
  Retrospective data; unproven benefits with known risks
  
  INR 1.5 – 2.5
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  INR 1.5 – 2.5
Other Management Issues

- Encourage steady exercise
- Immunizations
- Contraception
What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Oral CCB

Negative

Sustained Response

PAH Specific Therapies

Continue CCB

PAH-specific Therapies

Bosentan: Time to Clinical Worsening

**BREATHE-1**

- **Bosentan** (n=144)
- **Placebo** (n=69)

**EARLY**

- **Bosentan** (n=35)
- **Placebo** (n=13)

Event-free (%)

- **Bosentan**: 89% (p=0.0038)
- **Placebo**: 63% (p=0.0015)

Patients with no clinical worsening (%)

- **Bosentan**: 100% (p=0.0114)

Effect of Sildenafil on 6MWD

Change In 6MWD (m)

-20
-10
0
10
20
30
40
50
60
70

Placebo
20 mg of sildenafil
40 mg of sildenafil
80 mg of sildenafil

p < 0.001

Week
0 4 8 12

Inhaled Iloprost

Mean change from baseline (m)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=102)</th>
<th>Iloprost (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>-20</td>
<td>20</td>
</tr>
<tr>
<td>Week 8</td>
<td>-10</td>
<td>30</td>
</tr>
<tr>
<td>Week 12</td>
<td>10</td>
<td>20</td>
</tr>
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</table>

$p=0.004$
Survival with IPAH

Epoprostenol (n=41)

Conventional therapy (n=40)

Survival (%)

Week

$p=0.003^*$

**Side Effects / Cautions**

**ERAs**
Edema, Nasal congestion, Abnormal LFTs, Anemia, Teratogenic

**PDE5 Inhibitors**
Epistaxis, Headache, Dyspepsia, Flushing, Diarrhea, Visual changes, Hypotension (w/ nitrates)

**Prostenoids**
Flushing, Headache, Diarrhea, Nausea, Emesis, Jaw/Leg Pain, Hypotension, LH, Syncope, Delivery Site Complications (pain, infection, cough, thrombosis, infusion interruption)

**High Cost**
What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

Positive

Oral CCB

Sustained Response

No

Yes

Continue CCB

PAH Specific Therapies

<table>
<thead>
<tr>
<th>LOWER RISK</th>
<th>DETECTION</th>
<th>CLINICAL</th>
<th>DETERMINANTS OF RISK</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>Clinical</td>
<td>No</td>
<td>LOWER RISK</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression of symptoms</td>
<td>WHO class</td>
<td>HIGHER RISK</td>
</tr>
<tr>
<td>II, III</td>
<td>6MWD</td>
<td>Peak VO₂ &lt;10.4 mL/kg/min</td>
<td>PEAK VO₂ &gt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td></td>
<td>Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement</td>
<td></td>
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<tr>
<td>Peak VO₂ &gt;10.4 mL/kg/min</td>
<td>CPET</td>
<td>RAP &gt;20 mm Hg; CI &lt;2.0 L/min/m²</td>
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<tr>
<td>Minimal RV dysfunction</td>
<td>Echocardiography</td>
<td>Minimally elevated</td>
<td>BNP</td>
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## PAH-specific Therapies - US guidelines

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<th>WHO Class III</th>
<th>WHO Class IV</th>
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<tr>
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<td>ambrisentan po, bosentan po, epoprostenol IV, iloprost inh, sildenafil po</td>
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<tr>
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<td></td>
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Available in the Philippines – per PHAssociation International

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IPAH Survival with epoprostenol

n = 162

Survival

Months

% Survival

63%

35%

*p<0.001

Quality of Life in PAH

Domain Scores

Better QOL

US Population
Norm → 50

40

Worse QOL

Physical Function
Role-Physical
Bodily Pain
General Health
Vitality
Social Function
Role-Emotional
Mental Health

Summary Scores

Physical Component
Mental Component
PH INTERNATIONAL

PH Resources and Associations Worldwide
Medical Resources Worldwide
Resources Available by Language
International Faces of PH
Global Community Connection
PH Association Leaders' Corner
International PH News and Projects

GLOBAL COMMUNITY

Spotlight on...

There are thousands of pulmonary hypertension patients waiting to meet you!

Connect now

FEATURE VIDEO

Find a PH Association Near You

Resources Available by Language
PAH: Triumphs and Challenges

- Improved evaluation
- Improved therapy
- Improved exercise capacity
- Improved survival

- Delayed evaluation
- Cumbersome / Expensive Rx
- Residual Impairments
- No cure
- Still deadly