What’s New in Pulmonary Arterial Hypertension?

Agenda

5:00–5:30 AM  Registration and Breakfast

5:30–5:35 AM  Welcome and Introduction
Lewis J. Rubin, MD, FCCP (Chair)

5:35–5:50 AM  Review of Patient Case Presentation/Collection of Benchmark Outcomes Data
Lewis J. Rubin, MD, FCCP

5:50–6:10 AM  Classification of PAH
Richard N. Channick, MD, FCCP

6:10–6:30 AM  Diagnostic Modalities for PAH
Timothy L. Williamson, MD, FCCP

6:30–6:50 AM  Current and Future Approaches to Treatment of the Patient with PAH
Lewis J. Rubin, MD, FCCP

6:50–7:00 AM  Re-review of Patient Case Presentation/Collection of Post-education Outcomes Data and Concluding Remarks
Lewis J. Rubin, MD, FCCP
Learning Objective

• Describe changes or evidence for potential changes in recommendations for classification, diagnosis, and management of PAH
• Identify appropriate modalities used for diagnosing PAH
• Recognize the role of three current classes of medications that can be used to treat PAH and identify future therapeutic options

What’s New in Pulmonary Arterial Hypertension?

Case
Lewis J. Rubin, MD, FCCP
University of California, San Diego
La Jolla, California
A 35-Year-Old Woman with CTD and Dyspnea

- Prior serologic studies included a (+) ANA in a diffuse pattern and SCL-70, (-) Anti-DS DNA and RF
- Prior therapy has included periodic steroid pulses; presently she takes Prednisone 10 mg/d
- PMH and FH are unremarkable

Physical Examination

- P 90reg  BP 90/60  SpO₂ (RA) 93%
- Butterfly rash on face, diffuse telangiectasias
- Lungs with fine basilar rales and a high-pitched systolic murmur audible in both lung fields
- Heart with 3/6 systolic murmur and S₄
- Trace pitting pedal edema bilaterally
Diagnostic Studies

- Chemistries remarkable for Creat 2.2
- Hct 34, WBC 4,000, Plts 200,000
- ESR 40 mm/hr; complement normal
- CXR: cardiomegaly, small bilateral pleural effusions, basilar atelectasis or scarring
- ECG: right axis deviation, RVH with strain

Echocardiogram

- Small to moderate pericardial effusion
- RV hypertrophy and enlargement, with paradoxic septal motion. LV is small and appears underfilled
- Left atrial size is normal
- Severe tricuspid regurgitation with PA sys 100 mmHg
- Small right-to-left shunt detectable with agitated saline injection
High Resolution Chest CT

- Cardiac enlargement with pericardial effusion. Scattered mediastinal lymphadenopathy. Enlarged main pulmonary arteries. Diffuse mosaic pattern bilaterally consistent with alveolitis
What Would You Do Now?

A. Perform right heart catheterization
B. Perform thorascopic lung biopsy
C. Initiate therapy for ILD and/or pulmonary vasculitis with cyclophosphamide and prednisone
D. Order additional diagnostic tests
E. Do something else

Additional Testing Was Performed

- PFTs (%predicted): FEV₁ % 100%; TLC 70%; DL₅CO 35%
- 6-minute walk was 175m
- SpO₂ declined from 93% to 84% during 6MW
- Anti-phospholipid antibodies were positive
- Anti-thrombin-3, Proteins C and S levels were normal
What’s New in Pulmonary Arterial Hypertension?

Classification of PAH

Educational Support

Sponsored by the American College of Chest Physicians.

This educational activity is supported by an educational grant from Actelion.

This educational activity is supported by an educational grant from Gilead.
Faculty Disclosure

The ACCP remains strongly committed to providing the best available evidence-based clinical information to participants of this educational activity and requires an open disclosure of any relevant financial relationships that create a conflict of interest. It is not the intent of the ACCP to disqualify anyone from participating in this educational activity, but to resolve any conflicts of interest that may arise from financial relationships with commercial interests. All conflicts of interest are reviewed by the educational activity course director/chair, the Education Committee, and/or the Conflict of Interest Subcommittee to ensure that such situations are properly evaluated and, if necessary, resolved. The ACCP educational standards pertaining to conflict of interest are intended to maintain the professional autonomy of the clinical experts inherent in promoting a balanced presentation of science. Through our review process, all ACCP CME activities are ensured of independent, objective, scientifically balanced presentations of information. Disclosure of any or no relevant financial relationships will be made available on-site during all educational activities.

The following faculty member of this educational activity has disclosed to the ACCP that no potential conflict of interest exists with any respective company/organization, and this should be communicated to the participants of this educational activity:

Richard N. Channick, MD, FCCP
A 53-year-old woman has scleroderma and pulmonary hypertension. Her workup reveals diffuse pulmonary fibrosis with a total lung capacity of 50% predicted. Her right heart catheterization shows elevated pulmonary vascular resistance (500 dynes/sec/cm^5) and normal wedge pressure.

What is the classification category for this patient?

A. Group 1: PAH associated with connective tissue disease
B. Group 2: PH due to left sided heart disease
C. Group 3: PH due to interstitial lung disease
D. A and C
Which of the following disorders, when associated with pre-capillary PH, is not considered “Group 1 PAH”?

A. Portal vein thrombosis
B. Atrial septal defect
C. Systemic lupus erythematosus
D. Sarcoidosis

Hemodynamic Basics

• Pulmonary vasculature low pressure, low resistance
• Right ventricle non-muscular
• Acutely, mild increases in afterload can impair RV function
• Chronically, RV can compensate, develop ability to handle high pulmonary arterial pressures

\[
PVR \text{ (dynes/sec/cm-5)} = \frac{PAP_{\text{mean}} - PCW}{C.O.} \times 80
\]

\[
PAP_{\text{mean}} = PVR \times C.O. + PCW
\]
Dana Point Hemodynamic Definition of PH/PAH

**PH**
Mean PAP ≥ 25 mm Hg

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

What happened to Resistance?
ACC/AHA still includes PVR ≥ 2-3 wu


Clinical Classification of Pulmonary Hypertension (Dana Point 2009)

1. PAH
- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
- Associated with:
  - CTD
  - HIV infection
  - Portal hypertension
  - CHD
  - Schistosomiasis
  - Chronic hemolytic anemia

2. PH Owing to Left Heart Disease
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia
- COPD
- ILD
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms
- Hematologic disorders/splenectomy
- Systemic disorders
- Metabolic disorders
- Others

Modified Classification of PH: 5th World Symposium on PH

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 diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart disease (update)
      1.4.5 Schistosomiasis
      1.4.6 Chronic haemolytic anaemia

1. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1. PPHN

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

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. CTEPH

5. PH with unclear multifactorial mechanisms
   5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Pending publication.

Group 1: PAH

• Shared features:
  – Microarteriopathy to varying degrees
  – Often higher PVR, more RV dysfunction
  – Exclusion of significant “secondary” causes

• Differences:
  – Hemodynamic patterns (portopulmonary, CHD)
  – Natural history
Group 1: Pulmonary Veno-Occlusive Disease/PCH

- Characterized by pulmonary venular and capillary obstructions leading to a significant gas transfer abnormalities, increased lung congestion and, in severe forms, pulmonary edema
- Idiopathic or associated with other conditions, including scleroderma, hematologic malignancies, BMT, chemotherapy
- Degree of pulmonary hypertension variable

PVOD Imaging

- Varied features:
  - Interlobular septal thickening
  - GGOs
  - Adenopathy
  - Pleural effusions
Clues to PVOD

- Patient has PH which may not be severe
- Disproportionate hypoxemia and reduced $\text{DL}_{\text{CO}}$, in absence of PFO
- Chest CT with, sometimes subtle, abnormalities suggesting edema (nonspecific adenopathy, Gos)
- Hemoptysis on occasion, more common in large pulmonary vein stenosis
- Worsening gas exchange on ERA or $\text{PGI}_2$

Epidemiology of PH by Echo

- Single echo lab/Australian community of 160,000
- Etiology of PH noted on echocardiogram

- Left heart disease, 78.7%
- PAH, 2.3%
- Unknown, 6.8%
- CTEPH, 0.6%
- Lung disease, 9.7%
- Sleep-related hypoventilation, 1.9%
- Congenital heart disease, 1.9%

N = 483 of 4579 patients with echo PASP > 40 mm Hg

Gabbay E. Am J Respir Crit Care Med. 2007;175:A713.
Group 2: Left Heart Disease and PH

- Wide spectrum of pulmonary arterial response to pulmonary venous hypertension. “Out of proportion PH”: What is it?? “Overlaps 2 classifications”

Limitations of PCW Cutoff of 15

- PCW is a dynamic number, dependent on
  - Respiratory cycle
  - Volume
  - Heart rate
  - Position

How do we measure hemodynamics?
What Is the “True” PCW?

Group 3: Lung/Resp disease and PH.... Eg, COPD

- 7.4 % of patients with PH “out of proportion”
- May represent a treatable group
- PAP correlated with PaO\textsubscript{2} (Other studies show no correlation)

A Distinct Phenotype within Group 3?
63-year-old Male with hx SOB/PH

PFTs: Normal volumes and flows, markedly reduced DL\text{CO}.

Combined Emphysema/Fibrosis:
A Common Cause of PH

PH in 43% (median PAPm = 43 mmHg)

Survival of Patients With Combined Lung Disease

Survival (%)

Time (years)

- no PAH, systolic arterial pulmonary pressure < 45 mmHg
- PAH, systolic arterial pulmonary pressure ≥ 45 mmHg


Group 4: CTEPH

- Surgically treatable disease
- Classification challenges
  - “Distal” thrombus
  - Co-existing left heart disease
  - Lung disease
Challenges with Classification System

• Doesn’t account for patients with underlying heart/lung disease who also have PAH
• Many patients will “fit” a Group 1 diagnosis who may not be “true” Group 1 (older pts, borderline wedge pressure, mild to moderate lung disease)
• What are the cutoffs for “disproportionate” PH?

Summary

• A clinical classification system for pulmonary hypertension remains the standard
• Diseases within Group 1 (PAH) share many clinical and pathological features, but there are Important differences
• Pulmonary hypertension due to left heart disease remains the most common form of PH
• Some patients with underlying left heart and lung disease have “disproportionate” PH, although the classification of this phenotype is unclear
A 53-year-old woman has scleroderma and pulmonary hypertension. Her workup reveals diffuse pulmonary fibrosis with a total lung capacity of 50% predicted. Her right heart catheterization shows elevated pulmonary vascular resistance (500 dynes/sec/cm5) and normal wedge pressure.

**What is the classification category for this patient?**

- A. Group 1: PAH associated with connective tissue disease
- B. Group 2: PH due to left sided heart disease
- C. Group 3: PH due to interstitial lung disease
- D. A and C

**Which of the following disorders, when associated with pre-capillary PH, is not considered “Group 1 PAH”?**

- A. Portal vein thrombosis
- B. Atrial septal defect
- C. Systemic lupus erythematosus
- D. Sarcoidosis
What’s New in Pulmonary Arterial Hypertension?

Diagnostic Modalities for PAH

Educational Support

Sponsored by the American College of Chest Physicians.

This educational activity is supported by an educational grant from Actelion.

This educational activity is supported by an educational grant from Gilead.
Speaker

Timothy L. Williamson, MD, FCCP
University of Kansas Hospital
Kansas City, Kansas

Faculty Disclosure

The ACCP remains strongly committed to providing the best available evidence-based clinical information to participants of this educational activity and requires an open disclosure of any relevant financial relationships that create a conflict of interest. It is not the intent of the ACCP to disqualify anyone from participating in this educational activity, but to resolve any conflicts of interest that may arise from financial relationships with commercial interests. All conflicts of interest are reviewed by the educational activity course director/chair, the Education Committee, and/or the Conflict of Interest Subcommittee to ensure that such situations are properly evaluated and, if necessary, resolved. The ACCP educational standards pertaining to conflict of interest are intended to maintain the professional autonomy of the clinical experts inherent in promoting a balanced presentation of science. Through our review process, all ACCP CME activities are ensured of independent, objective, scientifically balanced presentations of information. Disclosure of any or no relevant financial relationships will be made available on-site during all educational activities.

Timothy L. Williamson, MD, FCCP
University grant monies
Industry sponsored multicenter research with Actelion and United Therapeutics
Grant monies (from industry-related sources)
Grant money for PH Symposium from Bayer/United Therapeutics/Actelion
Fiduciary position (of any organization, association, society, etc, other than ACCP)
Board of Directors, Comfort the Children, International
Consultation fee, speaker bureau, advisory committee, etc.
Advisory Board Faculty, United Therapeutics x 1 Wingman Advisory Program, United Therapeutics
Learning Objective

• Identify appropriate modalities used for diagnosing PAH
Goals of Diagnostic Testing

- Establish diagnosis/etiology of symptoms
- Assessment of exercise capacity
- Prognostic information
- Classification
  - Exclusion of CTEPH

Diagnostic Approach to PAH

Copyright ©2009 American College of Cardiology Foundation. Restrictions may apply.
## Assessment of Exercise Capacity

- **6MWT**
  - Predictive of survival in IPAH
  - Arterial desaturation > 10% during test increases mortality risk 2.9 X
  - 18% reduction in risk of death per 50m walked

- **CPET**
  - Peak VO$_2$ < 10.4 ml/kg/min is correlated with a worse prognosis
  - Reductions in VO$_2$ max, anaerobic threshold, and ventilatory efficiency


## Updated Classification of PH (5th WS Nice 2013)

<table>
<thead>
<tr>
<th>1. Pulmonary Arterial Hypertension</th>
<th>3. Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
<td>3.1 Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>1.2 Heritable PAH</td>
<td>3.2 Interstitial lung disease</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3</td>
<td>3.4 Sleep-disordered breathing</td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
<td>3.5 Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>1.3 Drugs and toxins induced</td>
<td>3.6 Chronic exposure to high altitude</td>
</tr>
<tr>
<td>1.4 Associated with:</td>
<td>3.7 Developmental lung diseases (Table)</td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</td>
<td></td>
</tr>
<tr>
<td>1.4.2 HIV infection</td>
<td></td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
<td></td>
</tr>
<tr>
<td>1.4.4 Congenital Heart diseases (table)</td>
<td></td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
<td></td>
</tr>
</tbody>
</table>

| 1’ Pulmonary Veno Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis |
| 1” PPHN |

<table>
<thead>
<tr>
<th>2. Pulmonary Hypertension Due to Left Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Left Ventricular Systolic Dysfunction</td>
</tr>
<tr>
<td>2.2 Left Ventricular Diastolic Dysfunction</td>
</tr>
<tr>
<td>2.3 Valvular disease</td>
</tr>
<tr>
<td>2.4 congenital/acquired left heart inflow/outflow tract obstruction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Pulmonary Hypertension with Unclear Multifactorial Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Hematologic disorders: Chronic hemolytic anemia myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td>5.2 Systemic disorders: Sarcoidosis, pulmonary histiocytosis, Lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>5.3 Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders</td>
</tr>
<tr>
<td>5.4 Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure, Segmental PH</td>
</tr>
</tbody>
</table>
Which is the preferred test for screening for presence of CTEPH?

A. Cardiac magnetic resonance imaging
B. V/Q scan
C. CT angiography
D. Invasive pulmonary angiography
E. Patients do not need to be screened for CTEPH

Ventilation-Perfusion Scan in CTEPH
Chronic Thromboembolic Pulmonary Emboli

What is the role of lung perfusion scan? Is pulmonary angiography still the gold standard for evaluating operability?

Task Force Recommendations

• VQ scan is recommended for diagnosis and mandatory for exclusion of CTEPH

• Selective pulmonary angiography remains the gold standard for evaluation of operability. In centers with particular imaging experience in CTEPH, high quality CT or MR pulmonary angiography may be an acceptable alternative for disease confirmation

• Referral to CTEPH team for operability assessment

Echocardiogram

- Chamber morphology
- Left ventricular systolic/diastolic function
- Exclusion of congenital heart disease
- Intra-cardiac (or pulmonary) shunts
- Valvular function
- RV function
- Estimation of PA pressure


ECHO vs RHC: Portopulmonary Hypertension Patients

Echo Parameters

A 47-year-old white female with scleroderma has 6 months of progressive dyspnea and LE edema. CXR and PFTs are normal. Echo demonstrates a moderately dilated RA and RV, and an estimated PA pressure of 70 mmHg. V/Q scan is negative. The next step should be to:

A. Initiate an oral pde-5 inhibitor
B. Start an inhaled beta agonist
C. Perform right heart catheterization
D. Refer patient to hospice

Cardiac Catheterization

**Definition of pulmonary artery hypertension:**

Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg

Pulmonary arterial occlusion pressure (PAOP) ≤ 15 mmHg

Catheterization is required for *every* patient with suspected pulmonary hypertension who will be treated

---

Should We Reintroduce PVR in the Definition of PH/PAH?

**Task Force recommendations on PVR**

- PVR should not become part of the general PH definition
- PVR should be included in the hemodynamic characterization of patients with PAH as follows: patients with PAH are characterized by pre-capillary PH (ie, PAPm ≥ 25 mmHg, PAWP ≤ 15 mmHg) and an elevated PVR (≥ 3 WU) in the presence of a normal or reduced CO
- In patients with high CO states (eg, cirrhosis, left-to-right shunt, SCD), a PVR ≥ 1.5 WU should be considered abnormal, but does not necessarily mean that the patient has PAH

*Harmonization of PVR units: The working group prefers the use of Wood units (WU), which can be directly derived from PAP, PAOP and CO measurements.*
How Do We Define and Handle “Borderline” PH?

- The upper limit of a normal mPAP is $20 \pm 2$ mmHg. PH is defined as mean PAP $\geq 25$ mmHg.

- A mPAP between 21 & 24 mmHg is not normal; in these cases it has been proposed to use the term of “borderline” PH.

- “Borderline” PH is frequently observed in Groups 2 and 3 however the meaning of this observation is unknown and has no therapeutic implications.

- “Borderline” PH is also observed in scleroderma patients screened for PH. Recent data support that a substantial number of these patients develop manifest PAH in the F-U.

Long-Term Follow-up of “Borderline” PH in Scleroderma

<table>
<thead>
<tr>
<th>Proportion with Pulmonary Hypertension (%)</th>
<th>Time to Pulmonary Hypertension (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.0</td>
</tr>
<tr>
<td>Borderline</td>
<td>0.0</td>
</tr>
<tr>
<td>Normal censored</td>
<td>0.2</td>
</tr>
<tr>
<td>Borderline censored</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Determine Pulmonary Vasodilator Reserve

- Establish the role of vasoconstriction
- Determine the potential for vasodilator therapy
- IV Adenosine, IV prostacycline, Inh NO
- Should be measured in most patients prior to initiating treatment?
Only 5% of IPAH Patients Benefit from CCB Long-Term


**Factors Related to Risk:**

### PAH Determinants of Prognosis

<table>
<thead>
<tr>
<th>Determinants of Risk</th>
<th>Lower Risk (Good Prognosis)</th>
<th>Higher Risk (Poor Prognosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class</td>
<td>II, III</td>
<td>IV</td>
</tr>
<tr>
<td>6MW distance</td>
<td>Longer (greater than 400 m)</td>
<td>Shorter (Less than 300 m)</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO$_2$ greater than 10.4 mL/kg/min</td>
<td>Peak VO$_2$ less than 10.4 mL/kg/min</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Minimal RV dysfunction</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP less than 10 mm Hg, CI greater than 2.5 L/min/m$^2$</td>
<td>RAP greater than 20 mm Hg, CI less than 2.0 L/min/m$^2$</td>
</tr>
<tr>
<td>BNP</td>
<td>Minimally elevated</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

Key Messages

• V/Q scan is the procedure of choice to exclude CTEPH

• Cardiac catheterization must be done to confirm diagnosis of PAH

Which is the preferred test for screening for presence of CTEPH?

A. Cardiac magnetic resonance imaging
B. V/Q scan
C. CT angiography
D. Invasive pulmonary angiography
E. Patients do not need to be screened for CTEPH

![Image of bar chart showing 97% for V/Q scan]
A 47-year-old white female with scleroderma has 6 months of progressive dyspnea and LE edema. CXR and PFTs are normal. Echo demonstrates a moderately dilated RA and RV, and an estimated PA pressure of 70 mmHg. V/Q scan is negative.

The next step should be to:

A. Initiate an oral pde-5 inhibitor
B. Start an inhaled beta agonist
C. Perform right heart catheterization
D. Refer patient to hospice

What’s New in Pulmonary Arterial Hypertension?

Current and Future Approaches to Treatment of the Patient with PAH
Educational Support

Sponsored by the American College of Chest Physicians.

This educational activity is supported by an educational grant from Actelion.

This educational activity is supported by an educational grant from Gilead.

Speaker

Lewis J. Rubin, MD, FCCP
University of California, San Diego
La Jolla, California
Faculty Disclosure

The ACCP remains strongly committed to providing the best available evidence-based clinical information to participants of this educational activity and requires an open disclosure of any relevant financial relationships that create a conflict of interest. It is not the intent of the ACCP to disqualify anyone from participating in this educational activity, but to resolve any conflicts of interest that may arise from financial relationships with commercial interests. All conflicts of interest are reviewed by the educational activity course director/chair, the Education Committee, and/or the Conflict of Interest Subcommittee to ensure that such situations are properly evaluated and, if necessary, resolved. The ACCP educational standards pertaining to conflict of interest are intended to maintain the professional autonomy of the clinical experts inherent in promoting a balanced presentation of science. Through our review process, all ACCP CME activities are ensured of independent, objective, scientifically balanced presentations of information. Disclosure of any or no relevant financial relationships will be made available on-site during all educational activities.

Lewis J. Rubin, MD, FCCP
Shareholder: Aires GeNO LLC
Consultant fee, speakers bureau, advisory committee, etc: Actelion, Gilead, NHLBI FDA, United Therapeutics, Lung LLC, Aires Pharmaceuticals, Bayer Schering Pharma, AG GeNO

Learning Objective

• Recognize the role of three current classes of medications that can be used to treat PAH and identify future therapeutic options
Which of the following statements is true?

A. Up-front combination therapy is superior to monotherapy in severely ill patients

B. The addition of sildenafil to epoprostenol improves exercise, hemodynamics, and survival

C. Doses of sildenafil higher than the approved dose (20 mg TID) produce improved hemodynamics and exercise capacity

D. Currently approved PAH therapies have also been shown to produce benefit in patients with PH due to left-sided heart failure

Choose the Correct Statement(s)

A. None of the currently approved therapies has been shown to improve survival

B. There is no evidence that treatment of PAH before moderate symptoms develop is of any benefit

C. Treatment guidelines suggest anticoagulation for all forms of PH

D. All of the above

E. None of the above
### 2013 – Algorithm

**Supervised exercise training (I-A)**
- Psychosocial support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal vaccination (I-C)

**General measures and supportive therapy**

**Expert Referral (I-C)**

**Acute vasoreactivity test (I-C for IPAH)** (IIb-C for APAH)

**Oral anticoagulants:**
- IPAH, heritable PAH and PAH due to anorexigenes (IIa-C)
- APAH (IIb-C)
- Diuretics (I-C)
- Oxygen* (I-C)
- Digoxin (IIb-C)

**Initial Therapy with PAH Approved Drugs**

### Initial Therapy

**Recommendation - Evidence**

<table>
<thead>
<tr>
<th>WHO-FC I</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>Ambrisentan, Bosentan, Sildenafil</td>
<td>Ambrisentan, Bosentan, Sildenafil, Epoprostenol iv, Iloprost inhaled</td>
<td>Epoprostenol iv</td>
</tr>
<tr>
<td>I-B</td>
<td>Tadalafil</td>
<td>Tadalafil, Treprostinil sc, inhaled</td>
<td></td>
</tr>
<tr>
<td>Ila-C</td>
<td>Epoprost iv, Treprostinil iv</td>
<td>Ambrisentan, Bosentan, Sildenafil, Tadalafil, Iloprost inhaled &amp; iv, Treprostinil sc, iv, inhaled, Initial Combination Therapy</td>
<td></td>
</tr>
<tr>
<td>IIb-B</td>
<td>Beraprost (Japan/S Korea)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---


---

Pathogenic Pathways and Treatment Targets in PAH


**Initial Therapy with PAH-Approved Drugs**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence*</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A or B</td>
<td>Ambrisentan, Bosentan, Macitentan***</td>
<td>Ambrisentan, Bosentan, Epoprostenol i.v., Iloprost inhaled</td>
<td>Epoprostenol i.v.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macitentan***</td>
<td>Iloprost inhaled, Macitentan***</td>
<td>Iloprost inhaled, and i.v. Macitentan***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riociguat, Sildenafil, Tadalafil</td>
<td>Riociguat, Sildenafil, Tadalafil, Treprostinil s.c., inhaled**</td>
<td>Riociguat, Sildenafil, Tadalafil, Treprostinil s.c., i.v, Inhaled*</td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td>Iloprost i.v., Teprotrin i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>B</td>
<td></td>
<td>Beraprost (Japan/S Korea)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td></td>
<td>Initial Combination Therapy</td>
<td>Initial Combination Therapy</td>
</tr>
</tbody>
</table>

---

*Level of evidence is based on the WHO-FC of the majority of the patients of the studies
**Approved only in the US
***NOT APPROVED COMPOUNDS

---

*J Am Coll Cardiol Suppl. In press.*
2013 – Algorithm

Initial Therapy With PAH Approved Drugs

Sequential combination therapy (I-A)

ERAs

Prostanoids

PDE-5 I or GCS

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Referral for Lung Transplantation (I-C)

Inadequate Clinical Response on Maximal Therapy

BAS (Ila-C)

PACES: Change From Baseline in 6-Minute Walking Distance (Meters)

**PACES-1: Pre-specified Subgroup Analysis According to Baseline 6MW**

<table>
<thead>
<tr>
<th>Category</th>
<th>&lt; 325 meters</th>
<th>&gt; 325 meters</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 75)</td>
<td></td>
<td>(n = 192)</td>
</tr>
<tr>
<td>6min WD (m)</td>
<td>-2.3</td>
<td>+38.4</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>+1.3</td>
<td>+0.6</td>
</tr>
<tr>
<td>Deaths</td>
<td>Placebo 7/34</td>
<td>Placebo 0/99</td>
</tr>
<tr>
<td></td>
<td>Sildenafil 0/41</td>
<td>Sildenafil 0/91</td>
</tr>
</tbody>
</table>


**Improved Patient Survival with Goal-Oriented Therapy**

Challenges for the Future

To develop:

• New and novel approaches to therapy
• New endpoints for clinical trials
• Meaningful/useful biomarkers
• Effective strategies for other forms of PH

Changes in PAH Trials Over Time

Given the changes in PAH treatment, short-term assessment of 6MWD may not be the best PAH trial endpoint in 2012.

Evolution From Exercise Capacity to Morbidity and Mortality RCTs

**6MWD Trials**
- Study 351: N = 32
- BREATHE-1: N = 213
- EARLY: N = 185
- ARIES-1: N = 202
- ARIES-2: N = 192
- SUPER-1: N = 277
- STEP: N = 67
- PHIRST: N = 405
- PACES: N = 267
- AIR: N = 203

**Morbidity and Mortality Trials**
- SERAPHIN
- GRIPHON: N = 742
- AMBITION: N = 545

New and Novel Treatments

- Enhance treatment strategies with currently available treatments
  - De Novo Combination v. Monotherapy (AMBITION)
Investigational Treatment Combinations for PAH

Front-Line Combination Therapy vs. Monotherapy

**AMBITION**
- Ambrisentan + Tadalafil
- Ambrisentan + Placebo
- Tadalafil + Placebo


### Investigational Treatments for PAH

<table>
<thead>
<tr>
<th>Targeted Pathway/Mechanism</th>
<th>Investigational Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin pathway</td>
<td>Selexipag</td>
</tr>
<tr>
<td></td>
<td>Oral Treprostinil</td>
</tr>
<tr>
<td></td>
<td>Beraprost MR</td>
</tr>
<tr>
<td>Endothelin pathway</td>
<td>Macitentan</td>
</tr>
<tr>
<td>Nitric oxide pathway</td>
<td>Riociguat</td>
</tr>
<tr>
<td>Growth factor signaling</td>
<td>Imatinib</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Cell therapy</td>
<td>Progenitor cells combined with gene therapy</td>
</tr>
</tbody>
</table>

FDA Approved October 2013
Macitentan for PAH

Phase III, randomized, double-blind, placebo-controlled study
N = 742
Maci 3 mg daily vs. Maci 10 mg daily

Phase III, open-label, long-term extension
N = 525
Maci 10 mg daily

SERAPHIN Has a Novel and Robust Morbidity/Mortality Primary Endpoint

A decrease in 6-MWD of at least 15%, confirmed by 2 tests on different days

Worsening of PAH symptoms, which must include either:
- An increase in FC, or
- Appearance or worsening of symptoms of RHF

Need for new PAH treatment(s):
- Oral or inhaled prostanoids
- Oral PDE-5 inhibitors
- ERA after study discontinuation
- Intravenous diuretics

Death
OR
Atrial septostomy
OR
Lung transplantation
OR
Initiation of i.v. or s.c. prostanoids
OR
Other worsening of PAH

Time to 1st morbidity or mortality event


Primary Endpoint: Morbidity and Mortality

No. at Risk
Placebo: 250 188 160 135 122 64 23
Macitentan, 3 mg: 250 213 188 166 147 80 32
Macitentan, 10 mg: 242 208 187 171 155 93 41

Macitentan 10 mg: Hazard ratio = 0.55; log-rank $P < 0.0001$
Macitentan 3 mg: Hazard ratio = 0.70; log-rank $P = 0.01080$


Targeting Pathways in PAH

Prostacyclin Pathway
NO/sGC/cGMP Pathway
Endothelin Pathway

Arachidonic acid
COX
Prostaglandins
L-Arginine
NOS
L-Citrulline
Pro-endothelin
ECE
Fragments

Riociguat (BAY 63-2521)
Endothelin
Endothelin-receptor antagonists
ET-A receptor
ET-B receptor

AC
Prostacyclin (PGs)
cAMP
GMP
PDEs
PDE5 inhibitor

Vasodilation and antiproliferation
Vasodilation and antiproliferation
Vasoconstriction and proliferation

Downregulation in PH
Upregulation in PH
### Endpoints in PATENT-1 with Riociguat

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Riociguat Individual titration</th>
<th>Placebo</th>
<th>LS-mean difference (95% CI)</th>
<th>Riociguat vs placebo; P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Week 12 change (±SD)</td>
<td>n</td>
<td>Week 12 change (±SD)</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>254 30±66</td>
<td>126 −6±86</td>
<td>26 (20 to 52)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR (dyn s cm⁻¹)</td>
<td>232 −223±260</td>
<td>107 −9±317</td>
<td>−226 (−281 to −170)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td></td>
<td></td>
<td>−432 (−782 to −82)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>WHO FC, improved/stable/deteriorated (%)</td>
<td>254 21/76/4</td>
<td>125 14/71/14</td>
<td>0.0033</td>
<td></td>
</tr>
<tr>
<td>Time to clinical worsening</td>
<td>254 −</td>
<td>126 −</td>
<td>0.0046</td>
<td></td>
</tr>
<tr>
<td>Borg dyspnea score</td>
<td>254 −0.4±2</td>
<td>126 0.1±2</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>253 0.03±0.2</td>
<td>124 −0.03±0.3</td>
<td>0.06 (0.01 to 0.1)</td>
<td>0.0660</td>
</tr>
<tr>
<td>LPH</td>
<td>247 −6±18</td>
<td>122 0.4±18</td>
<td>−6 (~10 to −3)</td>
<td>0.0019</td>
</tr>
</tbody>
</table>


### Phase 2 Selexipag Results on Primary Endpoint (PVR)

#### Per Protocol Analysis

![Per Protocol Analysis](image1)

#### All Treated Analysis

![All Treated Analysis](image2)

Phase 2 Selexipag Results
Secondary Endpoint (6MW)


Endothelial-Like Progenitor Cell (ELPC) Therapy in the Monocrotaline Model of PAH

Cell Therapy for PAH: PHACeT Clinical Trial
Progenitor Cells Combined with Gene Therapy

- Study design
  - Phase I
  - Open-label, dose-escalation study
- N = 18
- Treatment
  - Cells delivered via PA line over 3-day period
- Primary study endpoint
  - Safety and tolerability at 3 months


Future Therapies: Do We Have The Correct Targets?

- Rho kinase inhibitors
- Statins
- Elastase inhibitors
- Tyrosine kinase inhibitors
- Pyruvate Dehydrogenase Kinase Inhibitors (eg, Dichloroacetate)
- Transcription factor inhibitors (eg, HIF-1α or NFAT)
- Immunosuppressants
- Survivin inhibitors
- DHEA
- Vasodilator peptides (adrenomedullin, VIP)
- Cell cycle inhibitors (eg, rapamycin)
- Heparin
- Thiazolidinediones (eg, rosiglitazone)
- Angiopoietin 1 blockers
- Serotonin transporter/receptor blockers
- Gene and cell therapy (eg, eNOS, Kv 1.5, prostacyclin synthase, adrenomedullin, VEGF, BMPR-2)
Future Directions

• Targeting multiple pathogenic pathways
• Targeting new pathways
• Rho Kinase, VIP, Growth Factors
  Kv Channels
• Endothelial Cell Replacement:
  Stem/Progenitor Cells
• Genomic-based targeted therapy

Take Home Messages

• Pulmonary hypertension is not a disease, but a hemodynamic measure that is shared by many diseases
• Since management of these various conditions often differs, it is important to establish a correct diagnosis/etiology prior to embarking on a treatment strategy
Which of the following statements is true?

A. Up-front combination therapy is superior to monotherapy in severely ill patients
B. The addition of sildenafil to epoprostenol improves exercise, hemodynamics, and survival
C. Doses of sildenafil higher than the approved dose (20 mg TID) produce improved hemodynamics and exercise capacity
D. Currently approved PAH therapies have also been shown to produce benefit in patients with PH due to left-sided heart failure

Choose the Correct Statement(s)

A. None of the currently approved therapies has been shown to improve survival
B. There is no evidence that treatment of PAH before moderate symptoms develop is of any benefit
C. Treatment guidelines suggest anticoagulation for all forms of PH
D. All of the above
E. None of the above
What’s New in Pulmonary Arterial Hypertension?

Case
Lewis J. Rubin, MD, FCCP
University of California, San Diego
La Jolla, California

A 35-Year-Old Woman with CTD and Dyspnea

- Prior serologic studies included a (+)ANA in a diffuse pattern and SCL-70, (-) Anti-DS DNA and RF
- Prior therapy has included periodic steroid pulses; presently she takes Prednisone 10 mg/d
- PMH and FH are unremarkable
Physical Examination

- P 90reg    BP 90/60    SpO₂ (RA) 93%
- Butterfly rash on face, diffuse telangiectasias
- Lungs with fine basilar rales and a high-pitched systolic murmur audible in both lung fields
- Heart with 3/6 systolic murmur and S₄
- Trace pitting pedal edema bilaterally

Diagnostic Studies

- Chemistries remarkable for Creat 2.2
- Hct 34, WBC 4,000, Plts 200,000
- ESR 40 mm/hr; complement normal
- CXR: cardiomegaly, small bilateral pleural effusions, basilar atelectasis or scarring
- ECG: right axis deviation, RVH with strain
### Echocardiogram

- Small to moderate pericardial effusion
- RV hypertrophy and enlargement, with paradoxic septal motion. LV is small and appears underfilled
- Left atrial size is normal
- Severe tricuspid regurgitation with PAsys 100 mmHg
- Small right-to-left shunt detectable with agitated saline injection

### High Resolution Chest CT

- Cardiac enlargement with pericardial effusion. Scattered mediastinal lymphadenopathy. Enlarged main pulmonary arteries. Diffuse mosaic pattern bilaterally consistent with alveolitis
CT Angiogram
Mosaic Pattern

What Would You Do Now?

A. Perform right heart catheterization
B. Perform thorascopic lung biopsy
C. Initiate therapy for ILD and/or pulmonary vasculitis with cyclophosphamide and prednisone
D. Order additional diagnostic tests
E. Do something else

67%  28%  3%  0%  3%
Additional Testing Was Performed

- PFTs (%predicted): FEV₁ 100%; TLC 70%; DL₃₅% 35%
- 6-minute walk was 175m
- SpO₂ declined from 93% to 84% during 6MW
- Anti-phospholipid antibodies were positive
- Anti-thrombin-3, Proteins C and S levels were normal

What Would You Do Now?

A. Perform right heart catheterization
B. Perform thorascopic lung biopsy
C. Initiate therapy for ILD and/or pulmonary vasculitis with cyclophosphamide and prednisone
D. Order additional diagnostic tests
E. Do something else
Something Else Was Done

- VQ scan showed multiple mismatched segmental/lobar perfusion defects
- Pulmonary angiography confirmed severe pulmonary hypertension, with PA pressure 110/60 (mean 76 mmHg), and multiple vessels with webs, bands and partially occluded vessels, with some regions appearing avascular

Perfusion Lung Scan in the Patient With Unexplained Dyspnea
What’s New in Pulmonary Arterial Hypertension?