Management of Pulmonary Arterial Hypertension: Evolution in Management

Stephen C. Mathai, MD MHS
The Johns Hopkins Pulmonary Hypertension Program
Assistant Professor of Medicine
Johns Hopkins University
Disclosures

- Grant monies: National Institutes of Health/NHLBI Pulmonary Hypertension Association
- Consultant fee: Bayer HealthCare, Actelion
Learning Objectives

Medical Therapies in PAH: What do the WHO Proceedings and CHEST Guidelines Tell Us?

• Define the World Health Organization (WHO) Classifications of pulmonary hypertension

• Identify the necessary steps to appropriately diagnose patients with PAH earlier in the course of the disease

• Identify the pharmacologic therapies in PAH
Pre-Test Questions

Q 1. The Federal Drug Administration (FDA) has approved therapies for which of the following forms of pulmonary hypertension?

1. Pulmonary arterial hypertension
2. Pulmonary hypertension (PH) related to left heart disease
3. Chronic thromboembolic pulmonary hypertension
4. 1 and 3
Q 2. Selection of initial therapy for PAH should be based upon which of the following?

1. NYHA/WHO functional class
2. Mean pulmonary artery pressure
3. 6MW distance
4. How recently the agent was FDA approved
Case Presentation

• 45 year old female
• SLE diagnosed 4 years ago
• SLE complicated by severe Raynaud’s dz
  – Multiple digital ulcers treated with nifidipine
• Admitted 2 weeks ago for “purple toe,” dx= threatened digit loss
• Treated with alprostadil, nitrates
Case Presentation (continued)

Diagnoses:

- Severe pulmonary hypertension, WHO Group 1
- NYHA/WHO FC II (early)
- No RHF/preserved CO/normal RV on echo
- Pericardial effusion, probably SLE-related
- Severe Raynaud’s disease
- SLE
Case Presentation (continued)

Initiated PAH-specific therapy

- NO-active drugs (oral PDE-5 inhibitors or oral soluble guanylate cyclase stimulator)
- oral endothelin antagonists (ERAs)
- oral, IV, SQ, inhaled prostanoid
What the 5th World Symposium Statement and CHEST Guidelines Tell Us: The Five W’s

- Who
- Where
- What
- When
- Why
PH: Mean PAP ≥ 25 mmHg

Who?

PAH
- IPAH
- CTD
- PPHN, HIV
- Anorexigens

mPAP ≥ 25 mmHg
PCWP ≤ 15 mmHg
PVR > 3 Wood units

Treatment Guidelines

PAH

CTEPH*

Sickle Cell Disease from Group I to Group V

1. Left Heart Disease
   - HFrEF
   - HFpEF
   - Valvular

2. Multifactorial
   - Sarcoidosis

3. Respiratory Disease
   - Hypoxia

4. Thrombotic Embolic

5. Sarcoidosis

PH: Mean PAP ≥ 25 mmHg
PCWP ≤ 15 mmHg
PVR > 3 Wood units

Where?

• “We suggest that, whenever possible, all PAH patients be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy.”

• “…collaborative and closely coordinated care of PAH patients involving the expertise of both local physicians and those with expertise in PAH care.”

Grade of evidence: Consensus-Based

What? And When?

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I:</td>
<td>Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II:</td>
<td>Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
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<tr>
<td>Class III:</td>
<td>Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
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<tr>
<td>Class IV:</td>
<td>Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

What?
General Measures

• Prevent pregnancy $^{1,2}$
• Rehabilitation/Exercise $^1$
• Anticoagulation, diuretics, digitalis, oxygen $^1$
• Vaccination $^2$
• Air travel/altitude $^2$
• Surgery $^2$

$^1$ 5th Symposium
$^2$ ACCP Guidelines
Treatment Selection

• Based on Functional Class

• Differs based on status
  — Treatment-naïve
    • Relative stability vs. Rapid progression
  — Currently on therapy
    • Symptomatic vs. unacceptable or deteriorating clinical status
  — Patient preference

• Grading systems differ by report
### INITIAL THERAPY WITH PAH APPROVED DRUGS

**YELLOW:** Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.
†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea (beraprost).
‡ Positive opinion for approval of the CHMP of EMA

<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>Evidence or agreement</td>
<td>RCT/meta-analyses</td>
<td>Ambrisantan Bosentan Macitentan††&lt;br&gt; Riociguat†&lt;br&gt; Sildenafil Tadalafil</td>
<td>Ambrisantan Bosentan Epoprostenol i.v.&lt;br&gt; Iloprost inhaled Macitentan††&lt;br&gt; Riociguat†&lt;br&gt; Sildenafil Tadalafil Treprostinil s.c., inhaled†</td>
<td>Epoprostenol i.v.</td>
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<td></td>
<td>A or B</td>
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<td></td>
<td>Single RCT&lt;br&gt; Large CT</td>
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<tr>
<td>Weight in favor</td>
<td></td>
<td>Iloprost i.v. †&lt;br&gt; Treprostinil i.v.</td>
<td>Ambrisantan, Bosentan Iloprost inhaled and i.v†&lt;br&gt; Macitentan††&lt;br&gt; Riociguat†&lt;br&gt; Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†</td>
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<td>Consensus Registries</td>
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<tr>
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<td>Beraprost†</td>
<td>Initial Combination Therapy</td>
<td>Initial Combination Therapy</td>
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<tr>
<td>Less well established</td>
<td>C</td>
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<table>
<thead>
<tr>
<th>Grade/Evidence Recommendation</th>
<th>Benefits vs. Risk</th>
<th>Methodologic Strength of Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong/High: 1A</td>
<td>Clear benefit</td>
<td>Consistent RCT evidence; no limitations</td>
<td>Most patients Most situations</td>
</tr>
<tr>
<td>Strong/Moderate: 1B</td>
<td>Clear benefit</td>
<td>RCT with limitations</td>
<td>Most patients Most situations*</td>
</tr>
<tr>
<td>Strong/Low: 1C</td>
<td>Clear benefit</td>
<td>Flawed RCT with one critical outcome</td>
<td>Most patients Many situations</td>
</tr>
<tr>
<td>Weak/High: 2A</td>
<td>Balanced</td>
<td>Consistent RCT evidence Strong observational</td>
<td>Best action varies by patient</td>
</tr>
<tr>
<td>Weak/Moderate: 2B</td>
<td>Balanced</td>
<td>RCT with limitations Strong observational</td>
<td>Best action varies by patient</td>
</tr>
<tr>
<td>Weak/Low: 2C</td>
<td>Uncertain</td>
<td>Observational, case series, or RCT with major flaw</td>
<td>Other options reasonable</td>
</tr>
<tr>
<td>Non-graded: Consensus-Based</td>
<td>Uncertain, but expert opinion</td>
<td>Insufficient evidence</td>
<td></td>
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</tbody>
</table>
# Initial Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
<th>FC II</th>
<th>FC III</th>
<th>FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommend</strong></td>
<td>Grade 1B Grade 1C Grade 2C</td>
<td>Ambrisentan Sildenafil</td>
<td>Bosentan Ambrisentan Sildenafil</td>
<td></td>
</tr>
<tr>
<td><strong>Suggest</strong></td>
<td>Consensus-Based</td>
<td>Bosentan Macitentan Tadalafil Riociguat</td>
<td>Macitentan Tadalafil Riociguat IV Epoprostenol IV Treprostinil SQ Treprostinil</td>
<td>IV epoprostenol IV treprostinil Inhaled Iloprost or Treprostinil + Bosentan</td>
</tr>
</tbody>
</table>

### Combination Therapy

#### Sequential combination therapy (I-A)
- ERAs
- Prostanoids
- PDE-5i or sGCS

#### INADEQUATE CLINICAL RESPONSE

**Recommend**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
<th>FC III/FC IV Unacceptable/Deteriorating Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suggest</td>
<td>Consensus-Based</td>
<td>Oral + IV Epoprostenol IV/SQ/inhaled Treprostinil Inhaled Iloprost</td>
</tr>
</tbody>
</table>

#### INADEQUATE CLINICAL RESPONSE on MAXIMAL THERAPY

- Referral for LUNG TRANSPLANTATION (I-C)

#### CONSIDER ELIGIBILITY FOR LUNG TRANSPLANTATION

**BAS (IIa-C)**
When?
Clinical Worsening

• 5th Symposium:
  – WHO FC, exercise capacity, CI, RAP, NT-proBNP, echocardiographic parameters, perceived need

• ACCP Guidelines
  – No definition
Why?

- 5th Symposium: no specific goals
- ACCP Guidelines
  - Specific indications for each agent
    - Improve WHO FC
    - Improve 6MWD
    - Delay time to clinical worsening
    - Improve cardiopulmonary hemodynamics
Limitations

- Despite review of 8,256 citations identified by the ACCP Guideline literature search, how many of the 79 recommendations received an evidence grade (vs. consensus–based)?
  - 1. 63
  - 2. 22
  - 3. 35
  - 4. 9

To Be Determined...

• Order of initiation
  – ERA vs. NO-agent vs. prostacyclin
  – Initial combination vs. single agent

• Outcomes
  – Is all time-to-clinical worsening the same?
  – RV function parameter?

• Quality of life; Palliative care

• Other forms of PH?
Back to the Patient: Post Test Question

45 yo with SLE-PAH, WHO FC II symptoms with preserved RV function. Which of the following is not recommended or suggested as initial therapy according to the ACCP Guidelines?

1. Sildenafil
2. Ambrisentan
3. Inhaled iloprost
4. Macitentan
Summary: New Guidelines

• Applies only to adults with PAH
• Early referral to expert center and ongoing collaboration with local provider important
• Stratification by functional class for initial selection of therapy
• No recommendations for initial class of agent
• Combination therapy recommended for lack of clinical response to initial agent