Pulmonary Hypertension - Current Perspectives

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Pulmonary Hypertension –

• Characterized by
  – Restricted flow through the pulmonary arterial circulation
  – Result in increased pulmonary vascular resistance and raised pulmonary arterial pressure
  – Right heart failure – “endpoint”

• Life-threatening condition with a poor prognosis if untreated
Definitions:

• Mean PAP ≥25 mm Hg at rest or >30 mm Hg during exercise in the presence of a normal pulmonary capillary wedge pressure (≤15 mm Hg)

1\textsuperscript{st} World Symposium on Pulmonary Hypertension, Geneva, 1971

• Mean PAP ≥ 25 mm Hg at rest in the presence of a pulmonary capillary wedge pressure ≤ 15 mm Hg

4\textsuperscript{th} World Symposium on Pulmonary Hypertension, Dana Point, CA, 2008
Pulmonary Hypertension

• Is a “Disease of Triggers”
  • Genetic mutation / high LA pressure / hypoxia / obstruction

• Endothelial dysfunction is an early feature

• “Double Hit” theory
  1. Genetic predisposition: loss of function mutation of BMPR II & AKL-1
  2. Environmental factors – drugs, viruses or toxins
Predicted survival rates were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 231, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively. *Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.

Hemodynamics

- *In the NIH registry*, 3 hemodynamic variables were associated with an increased risk of death by univariate analysis:

  1. *Increased mPAP* (odds ratio [OR]: 1.16; 95% confidence interval: 1.05 to 1.28),

  2. *Increased mean right atrial pressure (mRAP)* (OR: 1.99; 95% confidence interval: 1.47 to 2.69), and

  3. *Decreased cardiac index (CI)* (OR: 0.62; 95% confidence interval: 0.46 to 0.82).
Survival by PAH Etiology

Prognosis in Mixed Treated/Untreated Cohorts

CHD = congenital heart disease; CVD = collagen vascular disease; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension; PoPH = portopulmonary hypertension.

The relationship between baseline mean pulmonary artery pressure (from less than 25 to more than 45 mmHg) and survival in patients with chronic obstructive pulmonary disease. Increasing pulmonary artery pressure was associated with a progressive decline in survival.

*Bishop, JM, Prog Respir Res 1975; 5:9.*
Impact of Functional Class on Survival

Correlation of Six-minute-walk Test and WHO Functional Class

*M* $p<0.05$ vs control subjects
†$p<0.05$ vs WHO functional class II
‡$p<0.05$ vs WHO functional class III

Correlation of Six-minute-walk Test With Survival in PPH

6-minute-walk distance strongly predictive of survival

- <332 m: 20% 3-year survival
- >332 m: 92% 3-year survival

Plasma BNP as a Prognostic Indicator of Mortality in Patients With PPH

Higher BNP at baseline (RR=11.971, \( p=0.0348 \)) and at follow-up (RR=25.880, \( p=0.0243 \)) were independent predictors of mortality.

## Table 2. 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>6MWT distance‡</td>
<td>Longer (greater than 400 m)</td>
<td>Shorter (less than 300 m)</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO₂ greater than 10.4 mL/kg/min</td>
<td>Peak VO₂ 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/m²</td>
<td>RAP greater than 20 mm Hg, CI less than 2.0 L/min/m²</td>
</tr>
<tr>
<td>BNP§</td>
<td>Minimally elevated</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

Reprinted from McLaughlin and McGoon (99). *Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions. †WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class. ‡6MWT distance is also influenced by age, gender, and height. §As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.

6MWT indicates 6-minute walk; BNP, brain natriuretic peptide; CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO₂, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.
Predicting Survival and Following Therapy

- Clinical parameters
  - functional class
  - exercise capacity
  - neurohormones
- Hemodynamics
- Imaging
  - right ventricle: function and size
  - pulmonary artery remodeling (future)
Screening and Diagnostic and Hemodynamic Assessment

• The diagnostic strategy for PH depends on the context in which it is employed:
  – 1) detection of a substrate in which the likelihood of a pulmonary vasculopathy may be heightened;
  – 2) discovery of the presence of PH;
  – 3) classification of the type of PH;
  – 4) confirmation of the presence of suspected PH; and
  – 5) determination of an appropriate treatment category
Algorithm for investigation of suspected pulmonary hypertension

Suspected pulmonary hypertension

Echocardiogram suggestive of pulmonary hypertension

No

Low clinical suspicion for pulmonary hypertension?

Yes

Seek alternative causes of symptoms

No

Consider:

Exercise echocardiogram
OR
Right heart catheterization

Yes

Significant left heart disease, adequate to explain pulmonary hypertension

Consider:

Pulmonary function tests
Overnight oximetry
Polysomnography
Ventilation-perfusion scan
ANA, RF, ANCA
HIV serology
Liver function tests

Underlying cause of pulmonary hypertension identified?

No

Idiopathic pulmonary arterial hypertension

Yes

Group 1 PAH, Group 3 PH, Group 4 PH, or Group 5 PH

Confirm with right heart catheterization

PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; ANA: antinuclear antibody; RF: rheumatoid factor; ANCA: anti-neutrophil cytoplasmic antibody.
Diagnosis PAH = RHC
Cardiac Catheterization to Assess Severity and Prognosis of PAH

- To measure wedge pressure or LVEDP
- To exclude or evaluate CHD
- To establish severity and prognosis
- To test vasodilator therapy

Catheterization is required for every patient with suspected pulmonary HTN.

LVEDP = left ventricular end diastolic pressure.
Treatment of Pulmonary Hypertension
Goals of Therapy

• Improve symptoms
  – 6-minute walk (>380 m)
  – functional class (I or II)
  – CPET (VO$_2$ max >10.4)
  – quality of life
• Improve hemodynamics
• Improve survival
General Measures

• Low level graded aerobic exercise - walking
• Avoid heavy physical exertion or isometric exercise
• Avoid exposure to high altitudes
  – Preflight SpO2 <92% should receive supplemental oxygen
• A sodium restricted diet (< 2,400 mg / day)
• Routine immunizations - influenza and pneumococcal pneumonia
• Current guidelines recommend that pregnancy be avoided or terminated early in women with PAH (30-50 % mortality)
PAH Treatments—a Historical Overview

CCB, anticoagulation, digitalis, diuretics

Epoprostenol

Bosentan

SC treprostinil

IV treprostinil

Iloprost

Sildenafil

Ambrisentan


CCB = calcium channel blocker.
Background Therapy

• **Anticoagulants**:
  - 3 non-controlled observational series in patients with primarily IPAH: improvement in survival
    - *NEJM 92, Chest 97, Circulation 84*
  - ACCF/AHA recommend warfarin in IPAH
    • **INR target of 1.5 - 2.5.**
  - Recommendations for patients with associated forms of PAH:
    • more advanced disease, such as those on continuous intravenous therapy, in the absence of contraindications.
Background Therapy

- **Diuretics** to manage RV volume overload
- **O2 supplementation** to maintain SpO2 >90%.
- **Digoxin in PAH**:  
  - One study demonstrated that the administration of iv digoxin in IPAH patients produced a modest increase in cardiac output and a reduction in circulating norepinephrine levels, although longer-term data are not available

  *Chest 1998;114:787–92*

  - Digoxin is used
  1. Patients with RHF & low CO
  2. Atrial arrhythmias
PAH

Basic therapy
Oral anticoagulants, Diuretics, O₂, Digoxin ...

Vasodilator study

Positive
Oral CCB
Sustained Response
Yes
Continue CCB

Negative
No CCB +++

Fall in mPAP > 10 mmHg
+ mPAP < 40 mmHg
+ Normal CO

Close monitoring of long-term clinical and hemodynamic effects

ACCP Guidelines. Chest 2004;126:1S-92S.
Survival in IPAH

Long-term CCB responders

Cumulative Survival

(Years)

0 2 4 6 8 10 12 14 16 18

Long-term CCB responders

p=0.0007

Long-term CCB failure

Use of calcium channel blockers in pulmonary arterial hypertension

Indications
- PAH patients with WHO group I and
- PAH diagnosis confirmed on right heart catheterization (i.e., PVR above 3.0 wood units by Fick’s method) and
- “Responder” on “acute vasoreactivity testing”

Contraindications
- Low cardiac output, cardiac index < 2.0
- Severe RHF
- Hypotension, systolic BP below 90 mm Hg
- History of adverse reaction or intolerance to CCB

Cautions
- Empiric trial of CCB without acute vasoreactivity testing should not be performed. It is unsafe and may cause hypotension [125] and even death [124]
- Acute vasoreactivity testing should not be performed with CCB because it is unsafe and may cause profound hypotension, acute pulmonary edema, and potentially death
- Patients who are acutely decompensated with RHF are not candidates for CCB therapy. There is no real reason to perform acute vasoreactivity testing in such patients
Use of calcium channel blockers in pulmonary arterial hypertension

Practical use of CCBs
Choice and dose of calcium channel blockers

- Chose nifedipine if baseline resting heart rate < 100/min and diltiazem if > 100/min
- Amlodipine may be used if significant side effects from other agents (e.g., worsening edema, significant tachycardia, bradycardia, or hypotension)
- Verapamil should not be used secondary to strong cardiodepressor effects
- Generally high doses are required (e.g., nifedipine up to 240 mg/d and diltiazem 720 mg/d, both in three divided doses, amlodipine up to 5 mg twice a day
- Only oral administration is used
Use of calcium channel blockers in pulmonary arterial hypertension

Initiation of CCB
CCB may be started in either inpatient setting or outpatient setting (there are no rigid recommendations, and approaches may vary among different centers)

A. Inpatient setting: rapid CCB dose escalation
   - All rapid CCB dose escalations are generally performed with PA catheter in place
   - Patients receive initial dose of nifedipine 10–20 mg orally or diltiazem 60 mg orally; hemodynamic measurements are obtained in 1 h
   - The dose and hemodynamic measurements are repeated every hour until a “threshold” response (fall in PVR by 50% and, not or, fall in mPAP by 33%) is achieved or significant side effects are experienced (eg, hypotension [mBP < 90 mm Hg], gastrointestinal upset [nausea, vomiting])
   - Total daily dose is calculated by adding up total amount of drug administered during this testing. The goal is to achieve this in three divided doses (four to six divided doses if significant side effects)
   - Patient is then given nifedipine 20 mg orally three times daily or diltiazem 60 mg orally three times daily next day and is discharged
   - The dose is then gradually increased to the desired level (as estimated previously) over a period of 6–12 wk while frequently monitoring BP and heart rate

B. Outpatient setting: slow CCB dose escalation

- Patients are started on initial dose of nifedipine 10–20 mg orally three times daily or diltiazem 60 mg orally three times daily
- The dose is then gradually increased with a goal to ultimately achieve the maximum dose (nifedipine 240 mg/d or diltiazem 720 mg/d, both in three divided doses; amlodipine up to 5 mg twice daily) over a period of 6–12 wk, while frequently monitoring the BP and heart rate. If patient experiences limiting side effects (as mentioned previously) before the maximum dose is reached, either the dose is kept at that level or further increase is achieved by increasing the dose frequency to every 4–6 h.
Use of calcium channel blockers in pulmonary arterial hypertension

Follow-up, when to use additional therapies

- Only 6.8% of all patients who have PAH are long-term responders to CCB (ie, who will be in NYHA I or II on monotherapy with CCB for 1 y) [32]
- Approximately half of the patients who are responders at initial acute vasoreactivity testing and are placed on CCB require an additional PAH therapy within 1 y
- Secondary to this risk of failure of CCB monotherapy, such patients should be closely followed (every 3–6 mo) and should be started on an additional therapy if there is clinical worsening or worsening of 6-minute walking distance.
- Secondary to this risk of failure of CCB monotherapy, some experts consider adding a specific PAH agent at the beginning, especially in patients who have poor predictors of long-term response at baseline hemodynamics and vasoreactivity testing [32]
PAH : Evidence-Based Treatment Algorithm
### Table 1: Quality of Evidence, Net Benefit, and Strength of Recommendation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of the evidence</td>
<td><strong>Good</strong> Evidence is based on good randomized controlled trials or meta-analyses.</td>
</tr>
<tr>
<td></td>
<td><strong>Fair</strong> Evidence is based on other controlled trials or randomized controlled trials with minor flaws.</td>
</tr>
<tr>
<td></td>
<td><strong>Low</strong> Evidence is based on nonrandomized, case-control, or other observational studies.</td>
</tr>
<tr>
<td>Expert opinion</td>
<td>Evidence is based on the consensus of the carefully selected panel of experts in the topic field.</td>
</tr>
<tr>
<td></td>
<td>There are no studies that meet the criteria for inclusion in the published reports review.</td>
</tr>
<tr>
<td>Net benefit</td>
<td><strong>Substantial</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Intermediate</strong></td>
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<tr>
<td></td>
<td><strong>Small/Weak</strong></td>
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<tr>
<td></td>
<td><strong>None</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Conflicting</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Negative</strong></td>
</tr>
</tbody>
</table>

### Table 2: Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Substantial</th>
<th>Intermediate</th>
<th>Small/Weak</th>
<th>None</th>
<th>Conflicting</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>A</td>
<td>A</td>
<td></td>
<td>B</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Fair</td>
<td>A</td>
<td>B</td>
<td></td>
<td>C</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Low</td>
<td>B</td>
<td>C</td>
<td></td>
<td>C</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Expert opinion</td>
<td>E/A</td>
<td>E/B</td>
<td>E/C</td>
<td>I</td>
<td>I</td>
<td>E/D</td>
</tr>
</tbody>
</table>
Prostacyclins

- Intravenous (epoprostenol, treprostinil)*
- Subcutaneous (treprostinil*)
- Inhaled (iloprost*, treprostinil†)
- Oral (beraprost‡)

*FDA approved
†Investigational/in development
‡Non-FDA approved
A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension


Abstract  Background. Primary pulmonary hypertension is a progressive disease for which no treatment has been shown in a prospective, randomized trial to improve survival.

Methods. We conducted a 12-week prospective, randomized, multicenter open trial comparing the effects of the continuous intravenous infusion of epoprostenol (formerly called prostacyclin) plus conventional therapy with those of conventional therapy alone in 81 patients with severe primary pulmonary hypertension (New York Heart Association functional class III or IV).

Results. Exercise capacity was improved in the 41 patients treated with epoprostenol (median distance walked in six minutes, 362 m at 12 weeks vs. 315 m at baseline), but it decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks vs. 270 m at baseline; P<0.002 for the comparison of the treatment groups). Indexes of the quality of life were improved only in the epoprostenol group (P<0.1).

Hemodynamics improved at 12 weeks in the epoprostenol-treated patients. The changes in mean pulmonary-artery pressure for the epoprostenol and control groups were −8 percent and +3 percent, respectively (difference in mean change, −6.7 mm Hg; 95 percent confidence interval, −10.7 to −2.6 mm Hg; P<0.002), and the mean changes in pulmonary vascular resistance for the epoprostenol and control groups were −21 percent and +9 percent, respectively (difference in mean change, −4.9 mm Hg per liter per minute; 95 percent confidence interval, −7.6 to −2.3 mm Hg per liter per minute; P<0.001). Eight patients died during the study, all of whom had been randomly assigned to conventional therapy (P=0.003). Serious complications included four episodes of catheter-related sepsis and one thrombotic event.

Conclusions. As compared with conventional therapy, the continuous intravenous infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe primary pulmonary hypertension. (N Engl J Med 1996;334:296-301.)
Long term outcome in IPAH


Epoprostenol

- **Indications**: NYHA Class III or IV PAH
- **Contraindicated in** severe LV systolic dysfunction (LVEF <30%) & in veno-occlusive disease
- **Cost**: ~ $60,000 to $120,000/year depending on dose
- **Continuous iv infusion**: Initial dose of 2 ng/kg/min >>>> optimal dose between 25 and 40 ng/kg/min for most adult
- **Side effects**: high cardiac output failure, headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Infections and infusion interruptions can be life-threatening
- **Half life**: 3-6 mts. Given as Continuous IV infusion via tunneled catheter. **Unstable at room temp & acidic pH**
Important Points: Epoprostenol

- Functional capacity, hemodynamics, and survival are improved
- Baseline NYHA functional class is predictor of survival
- Response after 12 to 18 months can predict subsequent outcomes
- Most benefit apparent in first 12 to 18 months
- Dosing: Outcomes with moderate dosing are the same as with aggressive dosing

IV epoprostenol in PAH associated with the scleroderma spectrum of diseases

- Multicenter, open label, randomized trial
- Marked improvements in exercise endurance and hemodynamics,
- No effect on mortality after 12 weeks of therapy.

• Observational series have also reported favorable effects of intravenous epoprostenol in patients with numerous forms of associated PAH
  
  – PH with associated congenital heart defects.  

  – HIV-associated pulmonary hypertension  
    *Am J Respir Crit Care Med.* 2003;167:1433–9

  – Secondary pulmonary *hypertension*  

  – Portopulmonary hypertension.  
SC Treprostinil

First studied in a 12-week, placebo controlled, multicenter, randomized trial of 470 patients with functional class II, III, or IV PAH (IPAH, connective tissue disease of CHD related)

modest but statistically significant increase of 16 m of the 6MW test, which was dose related.

CONCLUSION: chronic subcutaneous infusion of treprostinil is an effective treatment with an acceptable safety profile in patients with pulmonary arterial hypertension
Conclusions:
Long-term subcutaneous therapy with treprostinil appears to continuously improve exercise tolerance and symptoms in patients with PAH and inoperable CTEPH. Moreover, treatment may provide a significant survival benefit.
Conclusion: Subcutaneous treprostinil as a therapeutic option may improve outcome in pulmonary arterial hypertension. The safety profile for long-term subcutaneous treprostinil was consistent with previous short-term trials with no unexpected adverse events.
Treprostinil Sodium Injection

• Administered via continuous infusion using an ambulatory pump
• Given via self-inserted sc catheter
• Patients must have immediate access to backup infusion pump to prevent the risk of worsening of PAH symptoms due to interruption of therapy
• Dose 50-80 ng/kg/min
• Cost ~$60,000 to $120,000/year (exclusive of costs for administration/monitoring; IV more expensive)
• Requires capable patient

• Site pain is major impediment
  – Affects 85%
  – Local measures: ice, heat, lidocaine, capsaicin, collagenase ± effective
  – NSAIDs, narcotics, gabapentin ± effective
  – PLO gel topical; promising, but unconfirmed reports of benefit; not useful at active site

• Other common side effects include headache, diarrhea, rash, and nausea
IV Treprostinil

- Approved by FDA in January 2005
- Has safety (longer half-life: 4.5 hrs) and convenience advantages (no mixing or cold packs, smaller pump) over IV epoprostenol
- Can be used for de novo patients and transitions from epoprostenol
- Improvements in hemodynamics and functional status similar to epoprostenol
- Requires at least double the epoprostenol dose (may be more expensive)
Inhaled Iloprost

- Approved for class III - IV PAH
- Duration of hemodynamic effect only 90 minutes
- Requires frequent administration
- Has favorable effects on gas exchange in pulmonary fibrosis
- Cost of ~ $60,000-$70,000/year

Inhalational Iloprost


Inhaled Placebo

N=203
NYHA III or IV PAH, CTPH

2.5 or 5.0 ug (6 or 9 x/d, median 30ug/d)

Inhaled Iloprost

Baseline
12 weeks

Conclusion:
6-min walk distance improved (36 m, p=0.004)
NYHA class improved (p=0.03)

Dyspnoea improved (p=0.015)
Minimal improvement in hemodynamics

1° End-point
10% ↑6-min walk & improved NYHA Class w/o clinical deterioration or death
INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

Iloprost group mean baseline = 332 m
Placebo group mean baseline = 315 m

Placebo corrected mean difference at 12 weeks = 40 m (p=<0.01)

• In a study of 24 iloprost-treated IPAH patients, Hoeper et al. reported sustained benefits in exercise capacity and hemodynamics at 1 year.

• More recently, Opitz et al. reported event-free survival rates of 53%, 29%, and 20% at 1, 2, and 3 years, respectively, in IPAH patients treated with iloprost monotherapy.

• **Common side effects** of inhaled iloprost include cough, headache, flushing, and jaw pain.

• Iloprost was approved by the FDA in 2004 for functional class III and IV PAH

• Dose 2.5-5.0 mcg ampules via nebulizer, up to 12 times a day
Beraprost

- Oral analogue: half life 30-45 min
- *ALPHABET study* (RCT, double blind, multicenter): improved exercise capacity & symptoms but not the hemodynamics & functional class
- Approved in Japan only
Endothelin Antagonists (ERAs)

• Oral
  – “Nonselective” ERA/ERB
    • Bosentan*
  – “Selective” ERA
    • Ambrisentan*
    • Sitaxsentan†

*FDA approved
†Investigational/in development
The Endothelin System

Big ET-1 → ET converting enzyme → ET-1

↑ Circulating ET-1 levels in PAH
↑ PA endothelial cell expression in PPH

bosentan
sitaxsentan ambrisentan

ET_A

EC ET_B

SMC ET_B

Receptor

Smooth muscle cell vasoconstriction
Smooth muscle cell proliferation
? Apoptosis
Bosentan (Tracleer) Indication

- PAH with WHO Class III (or II - IV) symptoms
  “to improve exercise capacity and decrease the rate of clinical worsening”
- Dose 62.5 mg BID oral for 4 weeks
- 125 mg BID oral thereafter if liver functions OK
- Costs ~$36,000/year
- Contraindicated with glyburide and cyclosporine
BREATHE-1
Randomized double-blind, placebo-controlled

Mean change (±SE) in six-minute walking distance from baseline to week 16 in the placebo and bosentan groups

P<0.01 for the comparison between the 125-mg dose of bosentan and placebo, and P<0.001 for the comparison between the 250-mg dose and placebo by the Mann-Whitney U test. There was no significant difference between the two bosentan groups (P=0.18 by the Mann-Whitney U test).

Longer-term Study

McLaughlin et al. reported that first-line therapy with bosentan, with the addition or transition to other therapy as needed, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months.

At the end of 12 and 24 months, 85% and 70% of patients, respectively, remained alive and on bosentan monotherapy.


- Sitbon et al. compared survival in functional class III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol.
  - Kaplan-Meier survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated cohort and 91% and 84% in the epoprostenol cohort.

• **BREATHE-5 (Tracleer (Bosentan))**: multicenter, double-blind, randomized, and placebo-controlled study in Fc III Eisenmenger syndrome PAH:
  
  – Bosentan did not worsen oxygen saturation, and compared with placebo, bosentan reduced PVRI, decreased mPAP, and increased exercise capacity.

  *Galie N et al. Circulation 2006;114:48–54*

• Data with bosentan suggest clinical improvements in HIV patients with PAH & benefits in those with inoperable CTEPH and early stage disease
EARLY STUDY

• Bosentan has also recently been evaluated in a mildly symptomatic or functional class II population

• 168 PAH patients (IPAH, FPAH, PAH associated with connective tissue disease, anorexigen use, HIV, CHD) with a mean baseline 6MW test of 435 m were randomized to receive bosentan or placebo for 26 weeks.

• There was a significant improvement in PVR, but not in 6MW test.

• There was an improvement in the secondary end point of time to clinical worsening.

• The adverse event profile with bosentan was similar to previous studies
EARLY trial: Bosentan in NYHA class II

Bosentan Monitoring

- Liver enzymes: initial and monthly (stop if >5x elevation) reversible with cessation; can try rechallenge with lower dose
- Watch for leg edema/pulmonary edema/nasal congestion/testicular atrophy & male infertility
- Hemoglobin: initial, 1 and 3 months
- May interfere with hormonal birth control; barrier method advised
- Caveat: Response takes time (up to 2 to 3 months), should be used with caution in Class IV patients and not without right heart catheterization to document presence of PAH
Ambrisentan (Letairis) Indication

- PAH with WHO Class II - III symptoms
  “to improve exercise capacity and decrease the rate of clinical worsening”
- Dose 5 mg qD
- Consider increasing to 10 mg qD if tolerated
- Costs ~$36,000/year
- Contraindicated with cyclosporine
## Ambrisentan

<table>
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<th></th>
<th>ARIES-1</th>
<th>ARIES-2</th>
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<tbody>
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<td>Study</td>
<td>RCT, placebo-controlled phase III trials</td>
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<tr>
<td>Place</td>
<td>North America</td>
<td>Europe</td>
</tr>
<tr>
<td>Study population</td>
<td>202</td>
<td>192</td>
</tr>
<tr>
<td>Doses</td>
<td>Placebo or 5 or 10 mg of ambrisentan daily</td>
<td>Placebo, 2.5 mg, and 5 mg</td>
</tr>
<tr>
<td>Duration</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>6MWD</td>
<td>44-m improvement for the 10-mg dose and 23-m improvement for the 5-mg dose (p &lt; 0.05)</td>
<td>49 m and 22 m in the 5- and 2.5-mg daily dosage</td>
</tr>
</tbody>
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• Ambrisentan was FDA approved in June 2007 for PAH patients with functional class II and III symptoms.

• The incidence of transaminases elevations at 1 year was 2.8% in the clinical trials.

• Monthly monitoring of liver function tests, a monthly pregnancy test in women of child-bearing potential, and periodic hemoglobin measurements are required.

• Other potential side effects include lower extremity edema, which is more frequent (29%) and severe in patients over 65 years of age, and nasal congestion.

• Precautions regarding contraception and testicular atrophy are similar to bosentan.
PDE 5 Inhibitors

- Indicated in Fn class II & III
  - Sildenafil (tid dosing)
  - Tadalafil (advantage of single daily dose)

FDA approved 2005 & 2009
Sildenafil

- FDA approved in June 2005 for PAH (WHO Group 1) “to improve exercise ability” regardless of functional class
- Must not be used with nitrates, but compatible with other drugs
- Metabolized by liver (CYP3A4 isoenzyme), slowed in cirrhotics, no effect of renal failure
- Oral and relatively inexpensive (~ $12,000/year)
- The FDA-approved dose of sildenafil in patients with PAH is 20 mg administered orally 3 times daily.
- Side effects include headache, flushing, dyspepsia, and epistaxis, Blue haze periphery of vision in up to 11%
The SUPER-1 study
(Sildenafil Use in Pulmonary Arterial Hypertension)

- Randomized, double-blind, placebo controlled trial
- 278 patients with PAH (either IPAH or PAH associated with CTD or with congenital shunts) treated with placebo or sildenafil (20, 40, or 80 mg orally 3 times daily) for 12 weeks
- Mean placebo corrected increase in 6MD was 45, 46, & 50 m for 3 doses, respectively (p 0.001 for all comparisons)
- All sildenafil doses reduced the mPAP and improved Fn class
- Long-term data (available only at a dose of 80 mg 3 times daily) in 222 patients completing 1 year of treatment with sildenafil mono therapy showed sustained improvement from baseline at 1 year in the 6MW test (51 m).

Sildenafil in PAH: SUPER-1, 6-Minute Walk Test Change from Baseline to Week 12

Exercise Capacity at Week 12 and 1 Year

Tadalafil

- Approved in 2009 by FDA for PAH, 40 mg OD
- **PHIRST study**: 16-week, randomized trial
- 405 patients (either not received bosentan or receiving bosentan, and almost all with Fn class II or III)
- Doses of 2.5, 10, 20, and 40 mg were compared with placebo.
- Only with 40-mg dose significant improvement in the primary end point, 6MWD was seen
- In the patients who had not received bosentan, the increase was greater than in patients who were receiving bosentan (44 vs. 23 m).
- Tadalafil did not alter the WHO functional class but slightly prolonged the time to clinical worsening.

*Circulation 2009;119: 2894-903.*
Rationale for Combination therapy

- Increase treatment efficacy
- Reversal of treatment failure
- Targeting complementary signaling pathway
- Amplification of vasodilatation
- Prolongation of vasodilatory effect
- Augmentation of vascular anti-remodelling
Prostanoid and PDE-5

• PACES-1 trial (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil)
  – 267 patients with PAH who were being treated with a stable epoprostenol dose were randomized to receive either sildenafil or placebo.
  – Improvement in the 6MWT, hemodynamics and time to clinical worsening were demonstrated

Ann Intern Med 2008;149: 521–530
Prostanoid and PDE-5

- TRIUMPH-1 study (Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension)
  - Investigating inhaled treprostinil or placebo in combination with either bosentan or sildenafil or both.
  - Preliminary analysis results demonstrates improvement in 6MWT distance at 12 weeks in the treprostinil group; however, the results of combination remain to be published
Prostanoid and ETRA

- **STEP trial** (Safety and Pilot Efficacy Trial in Combination with Bosentan for Evaluation in Pulmonary Arterial Hypertension), a randomized, double blind, placebo-controlled trial looking at inhaled iloprost in combination with bosentan (n¼67), improvements were noted in 6MWT, NYHA functional status, and the time to clinical worsening.

- **COMBI trial** (COMbination therapy of Bosentan and aerosolized Iloprost), a smaller (n¼40) open-label study of similar duration, no improvement was noted in the 6MWD and NYHA functional class.
Limitations of Clinical Trials in PAH

• Many patients remain symptomatic, with a suboptimal quality of life and impaired hemodynamics despite treatment.

• With the exception of CCB in a robust responder, most therapies reduce PAP by 10% to 20%.

• A recent meta-analysis of 16 randomized trials in PAH found the following:

  1) a non significant reduction in all-cause mortality (relative risk 0.70, 95% confidence interval: 0.41 to 1.22);

  2) a significant improvement in exercise capacity as assessed by the 6MW test of 42.6 m (95% confidence interval: 27.8 to 57.8 m); and

  3) an improved dyspnea status by at least 1 functional class (relative risk 1.83, 95% confidence interval: 1.26 to 2.66) (161).
• These trials were all 8 to 16 weeks in duration.

• **None were powered to detect a survival benefit.**

• **More recently**, a meta analysis performed on 21 RCT (3140 patients) in PAH patients published through October 2008 reported improvements in the 6MW distance and a 43% decrease in mortality in patients treated with PAH-specific therapies versus patients randomized to placebo

  *(Eur Heart J. 2009;30:394–403).*

• A meta-analysis of the scleroderma spectrum of diseases related PAH patients included in 10 randomized controlled trials of oral therapy failed to demonstrate an improvement in exercise capacity in this subgroup *(Ann Rheum Dis. 2008;67:808–14).*

• This is contrary to the study of epoprostenol performed specifically in the scleroderma population, which demonstrated the greatest improvement in 6MW test ever reported in a clinical trial in PAH
Cost Considerations

- Clinical trials in PAH have not included analysis regarding cost/benefit ratio, quality-adjusted life years saved, or number needed to treat.

- The PAH-specific therapies are expensive.

  - The approx annual cost for sildenafil is $12761,
  - bosentan is $55 890,
  - ambrisentan is $56 736,
  - iloprost is $92 146.
  - epoprostenol is $33 153 and
  - treprostinil is $97 615.

- These costs may be much higher for larger patients and at higher doses
**Invasive Therapies**

- Despite advances in the medical treatment for PAH, many patients experience progressive functional decline, largely related to worsening right heart failure.

- In these patients interventional and surgical therapeutic options should be considered, including atrial septostomy and lung or combined heart and lung transplantation.

- In patients with PH caused by chronic pulmonary thromboembolism, surgical thromboendarterectomy may be beneficial.

- Other surgical approaches, such as RV mechanical assistance, are under investigation.
Atrial Septostomy

- Atrial septostomy creates a right to left inter-atrial shunt, decreasing right heart filling pressures and improving right heart function and left heart filling.

- While the created shunt decreases systemic arterial oxygen saturation, it is anticipated that the improved cardiac output will result in overall augmentation of systemic oxygen delivery.

- Improved cardiac output appears to be the principal hemodynamic benefit; magnitude from 15% to nearly 60%.

- Reported success rates for bridging patients to transplantation with septostomy range from 30% to 40%

- Procedural mortality is :15% based on published series (ranged from 5% to 50% in the different centers).
• Currently, atrial septostomy is recommended for patients with severe PAH and intractable right heart failure despite maximal medical therapy, including optimized PAH-specific agents and inotropes.

• The goals of the procedure are palliation and restoration and maintenance of clinical stability until a transplant can be performed.
Lung and Combined Heart and Lung Transplantation

• There is no agreement on the optimal type of transplantation for patients with PAH.

• While acceptable outcomes have been demonstrated with SLTx, many centers prefer DLTx to limit the reperfusion injury that has been reported in the donor lung of PAH patients undergoing SLTx.

• The combined procedure is generally reserved for patients

  • 1. with intractable right heart failure, especially when a patient has become dependent on inotropic support.

  • 2. also required in patients with PAH in complex CHD

  • 3. Also with PH and concomitant advanced left heart disease
Pulmonary Thromboendarterectomy

- Patients with suspected PAH should undergo evaluation for CTEPH.
- Patients are considered to be candidates for pulmonary thromboendarterectomy (PTE) if they have surgically accessible disease and present acceptable surgical risk.
- The goal of PTE is to remove sufficient material from the pulmonary arteries to substantially lower PVR and improve cardiac output.
Right Ventricular Assist Device

- Preclinical studies have suggested the usefulness of right ventricular assist device (RVAD) support in a model of PH (Biventricular support with the Jarvik 2000 ventricular assist device in a calf model of pulmonary hypertension. ASAIO J. 2004;50:444–50.).

- While a growing body of literature has emerged demonstrating the utility of RVAD support in patients with acute postoperative RV failure, often in the presence of PH, its utility in patients with PAH has not as yet been tested.
Other Investigational Therapies

• Inhaled NO

• NO/ nucleophile adducts eg DETA/NO >> Release NO when in contact with aqueous solutions. Effective when given intravenously. When given as aerosol, prolonged release of NO with long half life of >20 hours

• Increasing supply of substrate and co factors involved in the reaction >>

  1. L-arginine supplementation- usually in excess of 10gm/d

  2. Tetrahydrobiopterin

• NO donors- nitroglycerin, sodium nitroprusside, long acting oral nitrates
Other Investigational Therapies

- Statins (HMG co-reductase inhibitors): anti VEGF action
- K+ channel openers
- Rho kinase inhibitors
- Imatinib >> anti PDGF action
- Angiogenesis factors
- Gene therapy
  - NOS, K+ channel openers
- Serotonin receptor antagonists
- Inhaled vasoactive intestinal peptide
Early, Risk-based and Combination Therapy: Changing Paradigms for PAH?
Summary: Treatment

- Traditional therapies; diuretics, oxygen, phlebotomy still used as indicated; anticoagulants recommended

- Calcium Channel Blockers should be used in Class II or III acute responders but followed closely for safety & efficacy

- Newer agents are tailored to WHO class – ACCP Guidelines
  - Class IV – Infused prostacyclins
  - Class III – Oral endothelin receptor antagonists (ERAs), phosphodiesterase (PDE) 5 inhibitors, infused or inhaled prostacyclins
  - Class II – PDE 5 inhibitors, or ERAs
    - Consider therapy if evidence of Right Ventricular Dysfunction

- Combination therapies and an array of investigational therapies hold hope for the future

- Role of transplantation/septostomy now diminished because of new effective pharmacologic therapies
Indications for Referral to a Specialized Center for Rx of PAH

- Unexplained dyspnea on exertion with evidence of PH on Echo

- Evidence of moderate to severe PH
  - Estimated PAS pressure > 45 mm Hg on Echo
  - Symptoms consistent with NYHA functional class II or worse
  - Near-syncope or syncope

- Absence of substantial left sided cardiac disease or parenchymal lung disease

- Clinical or echocardiographic evidence of RV dysfunction
  - Lower-extremity edema
  - Ascites
  - Right ventricular enlargement or systolic dysfunction on echocardiography

Summary:

Use of Clinical Parameters, Hemodynamics, and Imaging Techniques to Predict Survival and Therapeutic Options

- High index of suspicion
- Thorough diagnostic evaluation, need RHC
- Exclude thromboembolic disease
- Vasodilator testing to eliminate inappropriate CCB use