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The mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA for:

- Developing and disseminating knowledge for diagnosing and treating pulmonary hypertension.
- Advocating for patients with pulmonary hypertension.
- Increasing involvement of basic and clinical scientists and practitioners.

More information on PHA’s Scientific Leadership Council and associated committees can be found at www.PHAssociation.org/SLC/
General Information

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned experts with the oversight of the Association’s Scientific Leadership Council. Its mission is to help physicians in their clinical decision making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in the peer-reviewed literature. Each article is reviewed and approved by members of the Editorial Advisory Board.

While most articles are invited by the editorial board, the following submissions will be considered for publication:

• Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
• Letters to the Editor
• Clinical case studies

Submitted manuscripts are reviewed by the editorial board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision making.

Manuscript Preparation and Submission Process

Submissions should be sent via e-mail as an attached Word document to the managing editor, Deborah McBride, at deb@msspubs.com. Manuscripts should be double-spaced and follow AMA style. Full-length manuscripts should not exceed 4,000 words including references. References should be limited to 50 entries. No more than 5 figures should accompany the manuscript. Accepted file formats are .gif, .tif, and .jpg. Each figure should be a separate file and figure legends should appear at the end of the manuscript. Each figure should be cited by number in the manuscript. Tables should be self-explanatory and details of the table should not be repeated in the manuscript. Tables should be prepared as part of the Word document. No more than 3 tables should be included with the manuscript. References should conform to AMA style and be numbered consecutively in the text. Reference numbers should be placed in parentheses at the end of the relevant sentence.

Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with AMA style.

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Conflict of Interest Disclosures

A statement of any and all grant, contract, and industrial support or proprietary interests of the author(s) related to the subject matter must be submitted with the manuscript.

Checklist

Authors should be certain to include the following with the manuscript:

1. Title page listing all authors with their academic degree(s) and affiliations.
2. Corresponding author contact information including e-mail and phone number.
3. Copyright release form signed by all authors
4. Conflict of Interest forms for all authors
5. List of approximately 5 key words for indexing purposes
6. Summary of the paper not exceeding 250 words in the format of Background; Objectives; Summary/Conclusions
Patients with pulmonary arterial hypertension (PAH) refractory to conventional pharmaceutical intervention with PAH-specific medications remain a significant challenge to providers. Generally, such patients are those who have failed combination therapy including infusion prostanoid. The presentation may be gradual decline or acute deterioration with right heart failure requiring critical care to resuscitate and stabilize the patient. Options for management entail a deliberate approach in PAH specialty centers and encompass complex interventions such as lung transplantation, atrial septostomy, Potts anastomosis, and bridging therapies such as extracorporeal circulation.

For that very reason, I am quite pleased that Dr. Harrison (who we all know as Hap) Farber accepted the gauntlet of challenge to serve as guest editor of the current issue. He has orchestrated a spectrum of articles and discussions that span the range of considerations for patients with refractory disease. I would also call your attention to the roundtable discussion that provides insight and perspective beyond the basic criteria for selection of patients for lung transplantation.

Unfortunately, patients may fail all medical interventions; therefore, guidance on the role of palliative care serves an important role. This issue includes 2 informative articles on this topic as well. Hopefully, the reader will be better equipped to care for these patients!

Charles Burger, MD
Professor of Medicine
Mayo Clinic College of Medicine
Medical Director, PH Clinic
Jacksonville, Florida

**GUEST EDITOR’S MEMO**

"Refractory pulmonary hypertension" is a phrase none of us in this field wants to hear. First, it means this patient is not doing well. Second, it makes us question our therapeutic approach: could I have done better; could I have been more aggressive with therapy; why did this patient fail? Yet, we know that, despite our best efforts, some patients with pulmonary arterial hypertension (PAH) will not “do well,” and we will be faced with the daunting task of how best to care for these patients.

In this issue of *Advances*, we address the options for the failing patient; hopefully, the following articles will better prepare you for this situation and will provide you with a blueprint of how to approach such a patient. In this issue, we discuss options such as lung transplantation, atrial septostomy, Potts anastomoses, bridging and mechanical therapies such as ECMO, and palliative care—all of which should be performed in a center with expertise in these complex entities.

I thank all those who contributed to this effort: the authors of the various articles and the participants in the Roundtable. In sum, I hope discussion of this difficult subject will make your PAH life a little easier.

Harrison Farber, MD
Professor of Medicine
Director, Pulmonary Hypertension Center
Boston University/Boston Medical Center
Boston, Massachusetts
At lunch before dinner before bedtime

The controlled clinical experience was limited to 12 weeks in duration. Treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor).

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled Treprostinil Sodium has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

Indication

Treprostinil (treprostinil) is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

Treatment sessions of ~2 to 3 minutes in length can be scheduled during waking hours and around daily activities, approximately every 4 hours.

Adding Treprostinil Sodium increased median 6MWD by 20 m (*P*<0.001) after 1.7 years (mean) on background therapy (sildenafil or bosentan).

Treprostinil was studied in TRIUMPH I, a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for ≥3 months before study initiation.

Patients were administered either placebo or Treprostinil Sodium in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) over the course of the 12-week study.

**Tyvaso can fit into their daily routine**

Common adverse events

The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%).

**INDICATION**

Tyvaso (treprostinil) is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

**IMPORTANT SAFETY INFORMATION FOR TYVASO**

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System.
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants.
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8, such as gemfibrozil, or inducers of CYP2C8, such as rifampin, are added or withdrawn.
- There are no adequate and well-controlled studies with Tyvaso in pregnant women. It is not known whether treprostinil is excreted in human milk.
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**References:**


TRIUMPH=TRIprost Finnish Multicenter Study. 


**Please see Brief Summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

For additional information about Tyvaso visit www.tyvaso.com or call 1-877-UNITHER (1-877-864-8437).
BRIEF SUMMARY

The following is a brief summary of the full prescribing information for TYVASO® (treprostinil) Inhalation Solution. Please review the full prescribing information prior to prescribing TYVASO.

INDICATIONS AND USAGE

TYVASO is a prostanoid vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Patients with Pulmonary Disease or Pulmonary Infections—The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Risk of Symptomatic Hypotension—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.

Patients with Hepatic or Renal Insufficiency—Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Risk of Bleeding—TYVASO inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

Effect of Other Drugs on Treprostinil—Co-administration of a cytochrome P450 3A4 (CYP3A) enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions:

• Decrease in systemic blood pressure
• Bleeding

Adverse Reactions Identified in Clinical Study—Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates observed in the postmarketing experience. The following adverse event has been identified during the postmarketing use of Tyvaso. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure: Angiodysplasia

Drug Interactions

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diolamine) and subcutaneously administered treprostinil (Remodulin®). Pharmacodynamics—Antihypertensive Agents or Other Vasodilators—Concomitant administration of TYVASO with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

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Unlock the combination of AMBITION

Please see Important Safety Information and Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
Unlock better outcomes with Letairis + tadalafil

Indication
Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. The study establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (58%) or PAH associated with connective tissue diseases (36%).

Important Safety Information
BOXED WARNING: EMBRYO-FETAL TOXICITY
- Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals.
- Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment.
- Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS program.

Contraindications
- Pregnancy: Letairis can cause fetal harm.
- Idiopathic Pulmonary Fibrosis (IPF), including IPF patients with pulmonary hypertension (WHO Group 3).
Improvements in BOTH long-term outcomes and functional capacity with initial combination therapy of Letairis + tadalafil

Significantly reduced the risk of disease progression
by 49% vs Letairis monotherapy ($P=0.0002$) and 45% vs tadalafil monotherapy ($P=0.0023$)*†

Significantly reduced the risk of hospitalization for worsening PAH
by 67% vs Letairis monotherapy ($P<0.0001$) and 56% vs tadalafil monotherapy ($P=0.0043$).
Of the primary endpoint components, only hospitalization for worsening PAH demonstrated statistical significance in patients treated with Letairis + tadalafil vs both monotherapies*‡2

Significantly improved median 6MWD from baseline at Week 24
(+43 m) vs Letairis monotherapy (+23 m) ($P=0.0004$) and vs tadalafil monotherapy (+22 m) ($P=0.0016$)*§2

*AMBITION trial design: A long-term, event-driven, randomized, double-blind, active-controlled trial where 605 patients with WHO Functional Class II or III PAH were randomized 2:1:1 to once-daily Letairis + tadalafil ($n=302$) or to Letairis ($n=152$) or tadalafil ($n=151$) alone. The primary endpoint was time to first disease progression event. Disease progression included death, hospitalization for worsening PAH, short-term clinical worsening, and inadequate long-term clinical response. 6MWD was a secondary endpoint.
†The percentage of patients who experienced a primary endpoint event was 20% with Letairis + tadalafil, 35% with Letairis, and 30% with tadalafil.
‡8% of patients receiving Letairis + tadalafil were hospitalized for worsening PAH vs 22% and 15%, respectively, in patients receiving Letairis or tadalafil.
§Baseline median 6MWD: Letairis + tadalafil=356 m, Letairis monotherapy=366 m, tadalafil monotherapy=352 m.

Important Safety Information (continued)

Warnings and Precautions

- **Embryofetal toxicity and Letairis REMS Program requirements:**
  - Prescribers must be certified with the program by enrolling in and completing training
  - All female patients, regardless of reproductive potential, must enroll in the Letairis REMS Program
  - Male patients are not enrolled in the program
  - Pharmacies must be certified with the program and must dispense to female patients who are authorized to receive Letairis

Further information is available at www.letairisrems.com or 1-866-664-5327.

- **Peripheral edema:** Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. Further evaluate patients who develop clinically significant fluid retention to determine the cause and possible need for edema treatment or to discontinue Letairis. In clinical studies, peripheral edema was more common with Letairis than with placebo (most edema was mild to moderate in severity); and with Letairis plus tadalafil than with either drug alone. There have also been postmarketing reports of fluid retention occurring within weeks after starting Letairis that required a diuretic, fluid management, or hospitalization for decompensating heart failure

- **Pulmonary edema with pulmonary veno-occlusive disease (PVOD):** Consider PVOD in patients who develop acute pulmonary edema during Letairis initiation and discontinue Letairis if PVOD is confirmed

- **Decreased sperm counts** have been observed in patients taking endothelin receptor antagonists and in animal fertility studies with ambrisentan. Counsel patients about potential effects on fertility

- **Hematologic changes:** Measure hemoglobin prior to initiation of Letairis, at 1 month, and periodically thereafter. Letairis initiation is not recommended for patients with clinically significant anemia. Consider discontinuing Letairis if clinically significant decreases in hemoglobin occur and other causes have been excluded. Decreases in hemoglobin and hematocrit have been observed within the first few weeks of Letairis treatment, which may persist during treatment. There have also been postmarketing reports of anemia requiring transfusion

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including **BOXED WARNING**, on the following pages.
Important Safety Information (continued)

**Adverse Reactions**

- Most common adverse reactions in combination with tadalafil compared to Letairis or tadalafil monotherapy were peripheral edema (45% vs 38% or 28%), headache (41% vs 34% or 35%), nasal congestion (19% vs 16% or 11%), cough (18% vs 13% or 16%), anemia (15% vs 7% or 11%), dyspepsia (11% vs 3% or 12%), and bronchitis (10% vs 4% or 9%)

**Drug Interactions**

- Cyclosporine increases ambrisentan exposure by 2-fold, limit Letairis to 5 mg once daily

**Use in Specific Populations**

- Breastfeeding: Choose Letairis or breastfeeding
- Hepatic impairment: Letairis is not recommended in patients with moderate or severe hepatic impairment. Fully investigate cause of liver injury in patients who develop hepatic impairment; discontinue Letairis if liver aminotransferases are >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded

**Dosage and Administration**

- **Adult dosage:** Initiate Letairis 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either increase Letairis to 10 mg or tadalafil to 40 mg, as needed and tolerated. Do not split, crush, or chew tablets.
- Pregnancy testing: Initiate Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment (see Contraindications, Warnings and Precautions, Use in Specific Populations).
- **Pregnancy testing:** Initiate Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment.

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following page.

**INDICATIONS AND USAGE:** Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening; and in combination with tadalafil to reduce the risk of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (34%).

**DOSAGE AND ADMINISTRATION:** See Contraindications, Warnings and Precautions, and Use in Specific Populations for additional information.

**Adult Dosage:** Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either increase Letairis to 10 mg or tadalafil to 40 mg, as needed and tolerated. Do not split, crush, or chew tablets.

**Pregnancy Testing in Females of Reproductive Potential:** Initiate treatment with Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment (see Contraindications, Warnings and Precautions, Use in Specific Populations).

**CONTRAINDICATIONS:** Pregnancy: Letairis may cause fetal harm when administered to a pregnant female. Letairis was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. (see Warnings and Precautions, Use in Specific Populations).

**Idiopathic Pulmonary Fibrosis:** Letairis is contraindicated in patients with idiopathic pulmonary fibrosis (IPF) including IPF patients with pulmonary hypertension (WHO Group III).

**WARNINGS AND PRECAUTIONS:** Embryo-fetal toxicity and Letairis REMS Program: For all females, Letairis is available only through a restricted program called the Letairis REMS because of risk of embryo-fetal toxicity (see Contraindications, Warnings and Precautions, Use in Specific Populations). Notable requirements of the Letairis REMS program include that the Prescribers must be certified with the program by enrolling in and completing training. All females, regardless of reproductive potential, must enroll in the Letairis REMS program prior to initiating Letairis. Male patients are not enrolled in the REMS. Females of reproductive potential must comply with the pregnancy testing and contraception requirements. (see Use in Specific Populations). Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis. Further information is available at www.letairisrems.com or 1-866-664-5327.

**Fluid Retention:** Peripheral edema is a known class effect of endothelin receptor antagonists (ERAs), and also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo (see Adverse Reactions). Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients. In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure. If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy. Peripheral edema/fluid retention is more common with Letairis plus tadalafil than with Letairis or tadalafil alone.

**Pulmonary Veno-occlusive Disease:** If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Letairis, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed Letairis should be discontinued.

**Decreased Sperm Counts:** Decreased sperm counts have been observed in human and animal studies with other ERA and in animal fertility studies with ambrisentan. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility (see Specific Populations).

**Hematological Changes:** Decreases in hemoglobin concentration and hematocrit have followed administration of other ERAs and were observed in clinical studies with Letairis. These decreases were observed within the first few weeks of treatment with Letairis, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Letairis in the 12-week placebo-controlled studies was 0.8 g/dL. Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving Letairis (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis. In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. Measure hemoglobin prior to initiation of Letairis, at one month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia. A clinically significant decrease in hemoglobin observed and other causes have been excluded, consider discontinuing Letairis.

**ADVERSE REACTIONS:** See BOXED WARNING and Warnings and Precautions for additional serious adverse reactions.

**References:**
Most adverse drug reactions were mild to moderate and only nasal congestion was dose dependent. Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%, 202/205) or placebo (13%, 137/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%, 165/564) compared to placebo (4%, 1/260). The results of such subgroup analyses must be interpreted cautiously. The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%, 5/261 patients) and placebo (2%, 3/152 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (0%) and for Letairis (5%, 13/261 patients). During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3x upper limit of normal (ULN) were 0% on Letairis and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

**Use in Combination with Tadalafil:** The mean exposure to Letairis + tadalafil in the AMBITION study was 79.7 weeks. The adverse reactions that occurred in >5% more patients receiving Letairis + tadalafil than receiving Letairis or tadalafil monotherapy in AMBITION are shown in Table 2.

**Adverse Reactions**

<table>
<thead>
<tr>
<th>Letairis + Tadalafil Monotherapy (N=302)</th>
<th>Letairis Monotherapy (N=152)</th>
<th>Tadalafil Monotherapy (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>13 (45)</td>
<td>58 (38)</td>
</tr>
<tr>
<td>Headache</td>
<td>125 (41)</td>
<td>51 (34)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>58 (19)</td>
<td>25 (16)</td>
</tr>
<tr>
<td>Cough</td>
<td>53 (18)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>Anemia</td>
<td>44 (15)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32 (11)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>31 (10)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

**Use in Patients with Prior ERA Related Serum Liver Enzyme Abnormalities:** In an open-label, open-study, 16 patients who had previously discontinued ERA therapy, an investigational drug, or both due to aminotransferase elevations >3x ULN were treated with Letairis. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5x ULN, but 9 patients had elevations >5x ULN. Eight patients had been re-challenged with bosentan and/or the investigational drug and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving protonatin or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow up of 12 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with readministration of previously used ERAs or show that Letairis led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced symptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

**Consult the full Prescribing Information for additional information regarding adverse reactions, including postmarketing events.**

**Drug Interactions:** Multiple coadministration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine.

**Use in Specific Populations:**

**Pregnancy Category X:** Risk Summary: Letairis may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications, Warnings and Precautions, Animal Data]. Letairis was teratogenic at oral doses of 25 mg/kg/day (AUC, 51.7 h·μg/mL) in rats and 27 mg/kg/day (24.7 h·μg/mL) in rabbits; it was not studied at lower doses. These doses are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h·μg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testis size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 15x, 31x, and 170x (on a mg/m2 body surface area basis) the maximum human dose of 10mg and an average adult body weight of 70 kg. These effects were absent at a maternal dosage of 17x the human dose based on mg/m2. Nursing Mothers: It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Letairis, a decision should be made whether to discontinue nursing or discontinue the drug to the mother.

**Pediatric Use:** Safety and effectiveness of Letairis in pediatric patients have not been established.

**Geriatric Use:** In the two placebo-controlled clinical studies of Letairis, 2% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (≥65 years) showed less decrease in liver function involvement when compared with Letirias than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

**Females and Males of Reproductive Potential:** Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy tests during treatment, and one month after stopping treatment with Letairis. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options [see BOXED WARNING and Dosage and Administration].

**Contraception:** Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine device [IUD], contraceptive implant, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception. Inform patients that regular counseling by another healthcare provider trained in contraception management is advised.

**Infertility:** Males In a 6-month study of another ERA, bosentan, 25 male patients with WHO functional Class III and IV PAH and normal sperm count were evaluated for effects on testicular function. There was a decline in sperm count at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed oligosperma at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or sperm concentration were noted. Based on these findings and preclinical data from ERAs, it cannot be excluded that ERAs such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility [see Warnings and Precautions].

**Renal Impairment:** There is no information on the use of Letairis in patients with mild or moderate renal impairment. There is no information on the use of Letairis in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

**Hepatic Impairment:** Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing hepatic impairment in liver function, however, exposure to ambrisentan may be increased in these patients. Elevation of Liver Transaminases: Other ERAs have been associated with aminotransferase elevations (AST, ALT) elevation, hepatotoxicity, and cases of liver failure [see Adverse Reactions]. In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if aminotransferase elevations >3x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded. Overdosage: There is no experience with overdose of Letairis. The highest single dose of Letairis administered to healthy volunteers was 1000 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdose could potentially result in hypotension that may require intervention.

For detailed information, please see full Prescribing Information. To learn more: call 1-800-GILEAD-5 (1-800-445-2236) or visit www.letairis.com. Manufactured and marketed by: Gilead Sciences, Inc., Foster City, CA 94404, USA ©2016 Gilead Sciences, Inc. All rights reserved. LETAIRIS 06/16
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Navigating the Road to Transplant in Pulmonary Arterial Hypertension: A Road Less Taken

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Dramatic advances in therapy for pulmonary arterial hypertension (PAH) in the last 20 years have improved survival from a median of 2.5 years in the pretreatment era to 7.5 years currently. However, impressive as that may seem, it is important to note that a median survival of 7.5 years is equivalent to that of surgically resected non-small cell lung cancer, thus underscoring the importance of lung transplantation as a treatment option in patients with PAH. In this edition of Advances, Edelman has reviewed the pathway to transplantation for patients with PAH, detailing the recommendations for timing of referral, listing for lung transplantation, the role of the lung allocation score in allocating a donor organ, and the outcome of lung transplantation.

The lung allocation score (LAS) was developed and implemented in May 2005. Prior to that, lungs for transplant were allocated largely based on time on the waiting list; such a system is an obvious disadvantage for patients with rapidly progressive or unpredictably progressive disease. Parameters used to assess disease severity (risk of death without a transplant) were tailored to the majority of patients awaiting lung transplantation, individuals who had some form of parenchymal lung disease (idiopathic pulmonary fibrosis [IPF] [United Network for Organ Sharing (UNOS) Group D], cystic fibrosis [Group C], chronic obstructive pulmonary disease [COPD] [Group A]). It was soon recognized that the success of the LAS in optimizing utilization of organs for those who would most benefit excluded patients with pulmonary arterial hypertension (PAH). Analysis of patients in REVEAL (the Registry to Evaluate Early and Long-term PAH Disease Management) identified risk factors predictive of mortality in patients with PAH (functional class III/IV, impaired renal function, elevated b-type natriuretic peptide, reduced 6-minute walk distance [6MWD], elevated right atrial pressure [RAP], presence of peri-cardial effusion, reduction in diffusion lung capacity for carbon monoxide). Unfortunately, the LAS did not reflect these risks for mortality. Another analysis from REVEAL in 2010 (5 years after introduction of the initial LAS) concluded that the LAS overestimated survival for patients who met criteria for listing for lung transplantation. The observed 1-year mortality exceeded that predicted by LAS in 2 subgroups of patients: those with mean RAP ≥14 mm Hg (14.8±1.9% vs 12.2%) and those with a 6MWD ≤300 m (17.3±1.7% vs 14.8%).

After reviewing these and other data, UNOS and the Organ Procurement Transplant Network (OPTN) permitted the ability to grant exceptions to patients with PAH based on severely reduced cardiac index and signs of right heart failure (elevated RAP ≥15 mm Hg). Additional indicators of hemodynamic compromise of other organs (rising bilirubin and increasing creatinine) have recently been added to the LAS rating. According to OPTN, these additions “...will further improve the survival prediction for all diagnostic groups; these effects will likely be most impactful for candidates in diagnosis Group B (PAH/pulmonary hypertension).” The effect of these revisions to the LAS will be analyzed in 3-5 years.

PAH is a rare disease and should represent a small proportion of patients undergoing lung transplantation. However, this disease affects a younger patient population than patients in Groups D and A, and the mean duration from diagnosis to death is second only to IPF (Group D). The LAS has improved organ utilization and coincided with an overall increase in the number of lung transplants per year. Yet, both the number and the percentage of those patients on the wait-list with a diagnosis of PAH have dropped steadily from 15.2% in 2004 (n = 579), to 11% in 2008 (n = 218), to 6.2% in 2013 (n = 99). The percent of patients with PAH actually transplanted in 2013 (3.8%, OPTN; n = 73) was less than the number of patients who were retrans-planted (4.1%; n = 79). Frankly, there is something seriously wrong with this.

Patients with PAH endure the longest time on the waiting list. Median wait time for candidates first listed in 2013 was 4.0 months: the shortest time was for COPD patients (2.6 months) and the longest time for PAH patients (9.7 months). PAH patients have the second highest mortality on the waiting list (second to group D patients with pulmonary fibrosis, who receive 54% of all lung transplants) (Figure 1).
A comparison of the likelihood of transplantation, death on the waiting list, and survival on the waiting list for PAH patients before and after implementation of the original LAS concluded that PAH patients were doing better since more patients were being transplanted by 5 years and fewer were dying on the transplant list (Figure 2). However, this does not consider the difficulty in obtaining wait-list status for these patients. In actuality, “better” is still not good! In this same study, only 42% of the wait-listed PAH patients were transplanted compared to 63% of all patients listed for lung transplant (28,183 listed and 17,687 transplanted).4

The perception of many PAH doctors, supported by currently available data, is that this generously donated resource is still not going to those most in need—by volume or disease severity. PAH physicians remain optimistic that recent changes implemented by UNOS/OPTN, innovations in donor optimization (eg, ex vivo lung perfusion), and organ retrieval following cardiac death may benefit patients when disease modification or mitigation fails. In the future, transgenic organ transplants and autotransplants utilizing 3-dimensional printer scaffolding may become available and help to remedy this enduring problem for PAH patients.

References
Navigating the Road to Transplantation for Pulmonary Arterial Hypertension

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Puget Sound VA Medical Center
Seattle, WA

Transplantation has been used to treat advanced lung disease successfully for more than 30 years. During this time, therapy for patients with pulmonary arterial hypertension (PAH) has evolved substantially. Along with changes in organ allocation, this has prompted alterations in the approach to referral and timing for transplantation for these patients. Functional and prognostic improvements attributable to PAH treatment have led to deferral or reduction in the need for transplantation for PAH. Nonetheless, for patients with conditions not responsive to treatment or those who experience disease progression despite maximization of medical PAH therapy, transplantation remains an important component of the therapeutic arsenal. In order to avail patients of transplant as an option for escalation in therapy, practitioners require familiarity with indications for timely transplantation referral, general criteria for listing or exclusion, as well as the US Lung Allocation Score (LAS) and other factors that affect waiting times and organ allocation for PAH patients.

This article will address the pathway to referral, waiting list placement, and transplantation for PAH patients. Double-lung transplantation (as opposed to heart-lung transplantation or single-lung transplantation) is currently the primary transplant procedure for PAH patients, and the majority who ultimately undergo this procedure are adults. There is international variability in the approach to organ allocation. This article will focus primarily on lung transplantation for PAH patients in the United States.

HISTORY
Successful heart-lung transplantation was first accomplished in 1981. The first 3 reported patients were transplanted due to PAH that was termed “primary pulmonary hypertension” (PPH) in 1 patient and complex congenital heart disease in the remaining 2. Single and bilateral lung transplants were accomplished in 1983 and 1986. While all 3 procedures have been utilized in the treatment of patients with advanced PAH, the current approach is to consider bilateral lung transplantation for most patients, with the utilization of heart-lung transplantation for patients with PAH in the setting of complex congenital heart disease or significant left ventricular dysfunction. Single-lung transplantation has been performed for PAH, but its current role in this setting is minimal due to risks and complications arising from the resulting profound mismatch of ventilation and perfusion.

Prior to May 2005, lung transplant waiting list priority was determined by “time accrued” on the list, so patients who were referred and listed at an earlier juncture in their disease course or who had less rapid disease progression had greater opportunity to receive organs. The Department of Health and Human Services’ Final Rule establishing requirements for broader sharing of organs and allocation based on medical urgency instead of waiting time went into effect in 2000. In response, the LAS was instituted in the United States in 2005. The multivariable model used to develop the LAS evaluated waiting list and post-transplant mortality. The mortality cohorts were composed of patients added to the lung transplant waiting list before 1999. The “PPH” cohort included 636 patients added to the waiting list from 1995 through 1998. Broad variation in waiting list mortality according to diagnosis was observed (chronic obstructive pulmonary disease [COPD] 13.8%, idiopathic pulmonary fibrosis [IPF] 33%, cystic fibrosis [CF] 28%, and PPH 30%), and diagnosis-specific risk factors for mortality were identified and incorporated into the model. The post-transplant mortality cohort of lung transplants performed from 1996 to 1999 included a total of 146 “PPH” patients. The LAS has made it feasible to transplant patients with more advanced and/or rapidly progressive disease and has had significant impacts on waiting list composition, wait times, mortality, and transplant numbers. Up
until a recent extensive revision, the LAS model had not undergone substantial alteration.

CURRENT TRANSPLANT VOLUMES AND OUTCOMES
The Organ Procurement and Transplant Network (OPTN) reports US national lung transplant volumes and outcomes. In 2014, 1925 lung transplants (45 for recipients ≤17 years of age) and 24 heart-lung transplants (6 for recipients ≤17 years of age) were performed. In the past 3 years, a total of 3 living donor lobar transplants have been reported in the United States. Approximately 3% of adult lung transplants, 40% of pediatric lung transplants, and 40% of heart-lung transplants were for PAH. Lung transplant procedure volumes for PAH as reported by the International Society for Heart and Lung Transplantation (ISHLT) are shown in Table 1.5

Six percent of approximately 1500 US patients listed for lung transplantation have PAH diagnoses. Current 1-, 3-, and 5-year survival rates after lung transplantation for PAH are 75%, 60%, and 48%.6 Recent median waiting times for all lung transplant patients have been in the range of 3.9 to 4.8 months, while those for PAH patients have ranged from 8 to 9.7 months. Wait-list mortality rates are 15 deaths per 100 wait-list years overall and 18 deaths per 100 wait-list years for PAH patients.7

Transplant volumes and waiting times reflect a scarcity of suitable donor organs. Before the implementation of the LAS in 2005, the annual volume of adult lung transplants was approximately 1000. This number increased after LAS implementation, with most recent volumes of 1898 in 2013, and 1880 in 2014.8 In recent years, efforts to expand the use and availability of donor lungs have included the use of expanded-criteria lung donors with and without ex-vivo lung perfusion (EVLP). The ISHLT Registry recently reported outcomes of 306 DCDD lung transplants with no difference in 1- and 5-year survival between DCDD (88% and 61%) and donation after brain death (DBD) (89% and 61%) recipients.8 In a single-center study, survival of 50 recipients receiving donor lungs from extended criteria or DCDD donors treated with EVLP showed no difference in 1-year survival compared with DBD recipients (87% vs 86%), and the authors estimated that use of EVLP led to a 10% to 15% increase in transplant volume.9 A follow-up study of 63 patients showed no difference in 1-, 3-, and 5-year survival, lung function, 6-minute walk distance (6MWD), or incidence of chronic lung allograft dysfunction compared with non-extracorporeal life support (ECLS) recipients.10

TRANPLANT INDICATIONS AND CONTRAINDICATIONS
The ISHLT guidelines suggest considering lung transplantation for adults with advanced lung disease portending a >50% 2-year mortality risk, but with an expected likelihood of post-transplant survival of >80% at 90 days and >80% at 5 years assuming adequate graft function. To minimize potential for delay in referral and in recognition of potential for prolonged or uncertain waiting times, these guidelines suggest transplant referral for patients with pulmonary vascular disease with any of the following: New York Heart Association (NYHA) Class III or IV symptoms during escalating therapy; rapidly progressive disease; use of parenteral PAH therapy; or known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis (Table 2). Listing for transplantation is suggested for patients who meet any of the following criteria: NYHA Class III or IV despite combination therapy including prostanoids; cardiac index of 2 L/min/m2; mean right atrial pressure >15 mm Hg; 6MWD of <350 m; development of significant hemoptysis, pericardial effusion, or signs of worsening right heart failure including renal insufficiency, rising bilirubin, rising brain natriuretic peptide, or recurrent ascites (Table 3).11 Referral in the setting of severely advanced disease or acute decompensation limits the likelihood of evaluation and listing for transplantation and increases the risk for adverse outcomes.12,13

Absolute contraindications to lung transplantation include: recent history of malignancy (disease-free interval of 2 to 5 years depending on type and recurrence risk); untreatable extrapulmonary organ dysfunction; uncorrected atherosclerotic disease with end-organ ischemia or dysfunction; acute medical instability; uncorrectable bleeding diathesis; chronic uncontrolled infection; significant chest wall or spinal deformity; body mass index >35 kg/m2; nonadherence to therapy; psychiatric or psychological barriers to care and adherence; lack of adequate social support; and severe functional limitations with poor rehabilitation potential.11 Additional relative contraindications cited are considered in the context of center-specific criteria as well as overall combined morbidities of individual patients.

The decision for referral and listing is multifaceted. Thresholds for timing of referral may vary according to treating practitioners’ experience and knowledge of transplantation and relationship with transplant centers to which they refer. Direct, frequent, and timely dialogue between referring and transplant programs is essential to make the overall process less daunting and confusing for patients, families, and providers. Transplant centers need to be informed of changes in the patient’s therapy and condition that might affect waiting list status.

<table>
<thead>
<tr>
<th>Table 1. Number of Transplants Overall and for PAH From 1995 to June 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-Lung Transplants (1995 to June 2014)</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Bilateral Lung Transplants (1995 to June 2014)</td>
</tr>
<tr>
<td>Heart-Lung Transplants (1982 to June 2014)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table 2. ISHLT Criteria for PAH Patient Referral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA Class III or IV during escalating therapy</strong></td>
</tr>
<tr>
<td><strong>Rapidly progressive disease</strong></td>
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<tr>
<td><strong>Use of parenteral PAH therapy</strong></td>
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<td><strong>Known/suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis</strong></td>
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NONPHARMACOLOGIC BRIDGES TO TRANSPLANTATION
Some patients with advanced and progressive disease despite medical therapy or with acute decompensation may be candidates for nonpharmacologic interventions that may serve as bridges to transplantation. Treatments including atrial septostomy (discussed in another article in this issue) and ECLS have been utilized to bridge PAH patients to transplantation. A recent series reported 46 balloon atrial septostomy procedures performed in 32 patients with significant functional limitations, right heart failure, or presyncopal or syncopal symptoms. The majority of patients were on multiple pharmacologic agents, and 54% were receiving infused prostanoids. Overall 1- and 5-year lung transplant-free survival rates were 66% and 44%. While the number of patients listed for lung transplantation was not reported, a total of 7 patients underwent lung transplantation at a mean of 760 days after septostomy.14 As with all patients where anatomic right-to-left shunting is present, perioperative management typically includes careful attention and monitoring, including intraoperative transesophageal echocardiography to minimize the risk of complications due to paradoxical embolism of air or thrombus. The anatomic shunt may be repaired at the time of transplantation.

Prioritization based on transplant urgency embodied in the LAS as well as advances in ECLS have increased the potential to obtain organs for critically ill patients requiring life support for circulatory and/or respiratory failure. In 2013, the OPTN reported that 14.1% of lung recipients aged 12 or over were in an intensive care unit (ICU) at the time of transplant, with 5.2%, 1.7%, and 3.1% supported by mechanical ventilation alone, ECLS alone, or the combination of mechanical ventilation and ECLS.7 As reported by the ISHLT Registry, hospitalization (including ICU hospitalization) at the time of lung transplantation is associated with a greater risk for 1-year mortality (hazard ratio [HR] 1.63), as is mechanical ventilation (HR 1.47).7 Similar registry data do not exist for patients supported with ECLS. Early experience with ECLS as a bridge to lung transplantation suggested a high 1-year mortality but good long-term outcomes in surviving patients. Patients being bridged to lung transplant with ECLS may have significant risks for critical illness myoneuropathy and prolonged mechanical ventilation including: systemic inflammation, corticosteroid use, neuromuscular blocking agents, diabetes, and immobility.15 A recent review of reported case series from 16 centers noted 1-year post-transplant survival for patients receiving ECLS as a bridge to transplant ranging from 33% to 100%.16 The largest reported single-center experience (26 patients) noted 1- and 2-year post-transplant survival of 68% and 53% for patients requiring ECLS as a bridge to transplant, compared with 85% and 79% for nonbridged patients. This series included 6 patients treated with awake ECLS who had a 100% survival at median follow-up of 10.8 months.16

Newer ECLS techniques do not require mechanical ventilation, permit patients to remain awake and ambulatory, and thus may reduce risks for prolonged ventilation and ICU stay after lung transplantation. Patients with pulmonary hypertension (PH) and right heart failure have been successfully bridged using venoarterial extracorporeal membrane oxygenation (ECMO) or through the use of a pumless oxygenator interposed between the pulmonary artery and left atrium and driven by pulsatile flow.17,18

ORGAN ALLOCATION
Allocation of lungs for candidates aged 12 and older is based on the LAS. This model categorizes patients into one of 4 lung-disease groups (Table 4): A – obstructive, B – pulmonary vascular, C – bronchiectasis, and D – restrictive. The LAS incorporates predictive models of 1-year waiting list mortality and 1-year post-transplant survival. Variables used in calculating the LAS are shown in Tables 5 and 6.19

If a program believes the LAS does not reflect a patient’s urgency for trans-
allocation, a request for approval of a specific priority or LAS may be submitted to the United Network for Organ Sharing (UNOS) Thoracic Organ Committee Lung Review Board (LRB). To compensate for the limited number of organ donors under the age of 12, programs may request that candidates less than 12 years of age be classified as adolescents to be eligible for allocation of adult lungs according to the LAS. Pulmonary hypertension patients deteriorating despite optimal therapy who have right atrial pressure >15 mm Hg or cardiac index <1.8 L/min/m² may qualify for LAS adjustment to the 90th percentile value if a request for this exception is submitted to the LRB. Referring and transplant centers should inform each other of patient deterioration and consider repeat right heart catheterization in anticipation of possible LAS exception. Exceptions to the LAS may also be considered in the setting of other factors that affect prognosis or waiting time, such as: significant hemoptysis, suspected diagnosis of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, or a high degree of allosensitization.

Lungs from donors aged 18 and over are allocated first to ABO-identical candidates aged 12 and over based on LAS, then to candidates under 12 years of age. Lungs from donors aged 12 to 17 are allocated first to recipients aged 12 to 17 based on LAS, then recipients under age 12, and then to recipients over the age of 17. Lungs from donors under 12 years of age are allocated first to recipients under age 12, then 12 to 17, then 18 and above. Candidates under the age of 12 receive a priority score of 1 or 2 based on medical urgency. Priority 1 criteria include: respiratory failure (continuous mechanical ventilation, supplemental oxygen requirement >50%, arterial pCO₂ >50 mm Hg, or venous pCO₂ >56 mm Hg) or PH (pulmonary vein stenosis involving 3 or more vessels, cardiac index <2 L/min/m², syncope, hemoptysis, or suprasystemic pulmonary artery pressure as assessed by catheterization or echocardiogram). As stated previously, recipients under age 12 can be granted an exception through the LRB to be classified as adolescents and be eligible for lung allocation based on LAS. Allocation of heart-lung blocks is driven by the highest-priority organ. When a heart-lung candidate is allocated a heart, the lung from the same deceased donor is allocated to the candidate. When a heart-lung candidate is allocated a lung, the heart from the same deceased donor is allocated to the candidate if no suitable Status 1A isolated heart candidates are eligible to receive the heart. Several notable trends have been evident since LAS implementation in 2005. There has been considerable regional variation in lung transplant rates and waiting times. There have been increases in: the total number of lung transplants; recipient age; and severity of illness as reflected by the LAS. The volume of transplants performed for patients with restrictive disorders (Group D) has increased, while volumes for groups A, B, and C have remained relatively unchanged. Group B waiting times increased dramatically in the first few years after the LAS was initiated. Although these times have subsequently declined, they have remained highest for all diagnosis groups at just under 10 months. After LAS implementation, Group B patients were shown to have the highest cumulative risk of death on the waiting list with the lowest likelihood of transplantation. While a small percentage of the overall waiting list, Group B patients have accounted for a disproportionate percentage of LAS exception requests (91 of 143 in 2013). The initial wait-list mortality data used in the development of the LAS was for “PPH” patients added from 1995 to 1998. This was an era during which new and effective therapies for PAH became available. During this period, the lung transplant waiting list was prioritized based on time accrued. Patients were listed in anticipation of potential for ongoing decline, often at the time that treatment was initiated. Many improved with treatment, leading to deferral of transplantation. Physiologic measurements at the time of listing used in the LAS model would have subsequently improved with treatment. Therefore, it is not surprising that these variables for PPH patients starting treatment did not accurately reflect the prognosis of subsequent PAH patients who were listed in the setting of deterioration despite medical therapy. Indeed, evidence from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) demonstrated that the LAS underestimated mortality for PAH patients with advanced disease as reflected by right heart failure (mean right atrial pressure 14 mm Hg) or exercise capacity (6MWD 300 m). These observations, combined with the high waiting list times and mortality rates for Group B patients, engendered concern as to whether the LAS appropriately prioritized these patients.

In February 2015, the LAS model was revised with the goal of more accurately reflecting current disease severity and post-transplant survival for candidates aged 12 and over. The waiting list model incorporated data for patients added from September 2006 through September 2008, while the post-transplant survival model used data for patients transplanted between May 2005 and September 2008. Validation analysis...
for these models included patients listed or transplanted in the subsequent 14 months. Changes included addition of new covariates as well as modification of previous covariates and their coefficients in the LAS equation. The addition of central venous pressure, cardiac index <2 L/min/m², creatinine, and bilirubin to the LAS model, as well as the treatment of 6MWD as a continuous variable and modification of other coefficients has the greatest effect on the LAS for Group B patients. The impact of this recent change on transplant waiting times, wait-list mortality, transplant volumes, and post-transplant survival will need to be assessed in the future.

CONCLUSION
Pulmonary arterial hypertension remains an indication for a small number of lung and heart-lung transplants annually. Areas for growth and improvement in transplantation include: identification of patients who are likely to benefit from transplantation; appropriate support of patients failing medical therapy; increasing donor organ availability; and prioritization of organ allocation to minimize wait-list mortality and maximize post-transplant survival. Recent PAH registry studies such as REVEAL have enhanced our ability to assess prognosis. Knowledge of transplant referral and listing criteria as well as communication between PAH and transplant programs is necessary to determine when transplantation is appropriate and feasible. Techniques including ECLS to bridge patients to transplantation and EVLP and DCDD to improve donor organ availability continue to evolve. The 2005 LAS did not achieve its goals for PAH patients as evidenced by the persistent high wait-list mortality, low rate of transplantation, and frequent need for LAS exceptions. Recent LAS revisions should more accurately reflect wait-list mortality and transplant benefits for current PAH patients. The changes in PAH therapy and transplantation will need to be evaluated on an ongoing basis to determine their impact and identify areas for future refinement.

References
Balloon Dilation Atrial Septostomy and Potts Anastomosis for Severe Pulmonary Arterial Hypertension: Why, When, and How

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Despite advances in pharmacologic treatment, pulmonary arterial hypertension (PAH) remains a fatal disease. In recent years, surgical/interventional approaches including balloon dilation atrial septostomy and Potts anastomosis have been applied to improve the hemodynamic variables associated with right ventricular failure in the setting of PAH. These interventions may improve quality of life and prolong survival in this population. In this review, we will discuss the role of these 2 therapeutic alternatives in the management of PAH.

ATRIAL SEPTOSTOMY
Background and Rationale
There is both clinical and experimental evidence suggesting that, in the setting of PAH, an interatrial right-to-left shunt may be of benefit. From a clinical standpoint, we know that PAH patients with a patent foramen ovale survive longer than those without one.7 We also know that Eisenmenger patients with a comparable degree of pulmonary hypertension (PH) survive longer and do not develop severe RV dysfunction when compared to patients with PAH, reflecting better RV performance in Eisenmenger’s physiology.8,9 The first study exploring and supporting the role of interatrial shunts in PAH was published by Austen et al almost 50 years ago.10 This study is extraordinary, not only because it demonstrated that the surgical creation of an atrial septal defect (ASD) in the setting of experimental RV...
hypertension provided hemodynamic benefit at rest and during exercise, but also because it described most of the knowledge we now possess regarding the physiological changes caused by atrial septostomy in the setting of PAH. In his original publication, Austen proposed that the surgical creation of an ASD should be performed for the management of patients with “primary” pulmonary hypertension (PPH).10 Interestingly, this operation never took place in part because years later, nonsurgical creation of an ASD for the management of CHD (ie, transposition of the great arteries) was successfully achieved by Rashkind5 and Park.6

Continuous improvements in transcatheter techniques to create an ASD became an attractive alternative in the setting of human PAH. In 1983, Rich and Lam13 were the first to perform this intervention. The rationale was that clinical deterioration and death in PPH were associated with obstruction to systemic flow and dilation and failure of the RV, thus creation of an ASD in this context would allow a right-to-left shunt to increase systemic output and allow for decompression of the right chambers, alleviating RVF. Initial case series published in the early 1990s12-14 appeared to confirm this hypothesis and showed promising hemodynamic benefits for PAH patients, albeit with a high procedure-related mortality. Hence, recommendations to minimize procedure-related mortality were made at the World Symposium on PH in 1998,15,16 and have remained since.

Procedure

The technique of atrial septostomy has evolved over time and has undergone minor modifications by performing centers. At present, balloon dilation atrial septostomy (BDAS) is the preferred technique.14,17 It involves a standard right and left heart catheterization; baseline right and left heart pressures are recorded simultaneously and cardiac output is calculated by Fick method. Following baseline hemodynamic assessment, standard trans-septal puncture is performed using a Brockenbrough needle and a Mullins-type dilator. In recent years, the use of intracardiac echocardiography has been advocated to acquire better visualization of the atrial septum to guide trans-septal puncture.18 In addition, radiofrequency-assisted perforation of the atrial septum has been described as a safe and feasible alternative to conventional needle puncture.19 Once access into the left atrium is gained, the septostomy orifice is sequentially dilated using noncompliant peripheral balloons in a carefully graded step-by-step manner, beginning with a 4 mm diameter balloon, followed by dilation with an 8 mm, 12 mm, and 16 mm balloon if needed (Figure 1). Between each step and after a 3-minute waiting period allowing hemodynamic stabilization, left ventricular end-diastolic pressure (LVEDP) and arterial oxygen saturation ($\text{SaO}_2$) are obtained. The final diameter of the ASD is reached on an individual basis when any of the following criteria are met: 1) LVEDP increase to $\geq 18 \text{ mm Hg}$; 2) decrease in $\text{SaO}_2$ to 80% or below; or 3) a 10% $\text{SaO}_2$ decrease from baseline. Post-procedure care requires a stay in the intensive care unit for at least 48 hours, where continuous supplementary oxygen is delivered and appropriate anticoagulation is started. Upon hospital discharge, all patients are followed as outpatients, with particular attention to maintaining effective oral anticoagulation and appropriate hemoglobin levels.14,17

Worldwide Experience

Proper appreciation of the role of atrial septostomy in the management of PAH has been limited mainly by the lack of controlled clinical trials demonstrating its efficacy and safety. Most of our knowledge regarding the procedure comes from small series of patients or case reports. In addition, the relative success of current pharmacologic strategies, as well as the notion of a previously reported high procedure-related mortality12,13,20 have prevented widespread use of this valuable intervention. Despite these limitations, experience with atrial septostomy has increased in the past few years.

In a recent worldwide experience review,21 372 procedures performed in 324 patients were identified; 304 had been reported in case series and another 20 as case reports. This experience is further enriched by the recent report of 85 procedures performed in 63 patients reported in 4 series22-25 and 3 more reported as case reports,18,26,27 showing similar results. These studies demonstrate that atrial septostomy has largely been performed in young people (mean age 31 years), mostly women (~70%), and in patients with idiopathic PAH (IPAH) in functional classes III and IV (~77%). In a significant proportion, BDAS has been performed in patients with refractory CHF and recurrent syncope despite maximal medical treatment. In this context, BDAS is the procedure of choice, and the size of the defect usually varies from 8 to 18 mm, with a mean value of approximately

Figure 1: Balloon dilation atrial septostomy. After perforation of the septum with the Brockenbrough needle, a circular-end guidewire is positioned in the left atrium. An initial dilation of the atrial septum is done with the Inoue dilator (left panel), and concluded with balloons of different sizes (right panel) in a step-by-step manner.
11 mm. A large majority of patients (~86%) survive the procedure, with 90% of patients describing improvement in symptoms and functional capacity. Furthermore, approximately 13% of patients received a lung transplant at some point after the procedure.²¹

Overall procedure-related mortality is 14%, with 8% occurring within the first 24 hours due to refractory hypoxemia and an additional 6% occurring within the first month post-intervention. Baseline right atrial pressure (RAP), in particular RAP >20 mm Hg, remains the most significant risk factor for procedure-related mortality.²⁶ Low SaO₂ (<90%) following intervention, perhaps in relation to an oversized septostomy, has also been associated with higher risk of death.²¹ Technical expertise and experience with the procedure also contribute to mortality, as reflected by lower mortality reported in recent series.²²,²³,²⁹

The hemodynamic effects of an atrial septostomy depend highly on the baseline RAP. Table 1 shows how a higher baseline RAP will result in a more pronounced hemodynamic effect, particularly when RAP >20 mm Hg (ie, severe RVF). However, as previously mentioned, patients with RAP >20 mm Hg will also have a significantly higher risk of death during the procedure as a result of refractory hypoxemia. Thus, it appears that the best risk-benefit ratio corresponds to the group with RAP between 10 and 20 mm Hg. Nevertheless, it should be noted that even when RAP is <10 mm Hg (predominantly patients presenting with syncope), there is a significant increase in CI as well as an improvement in functional class, suggesting that septostomy at an earlier stage of disease could be beneficial.²¹ It is also important to note that most of the hemodynamic variables reported have been obtained during the resting state and that the hemodynamic impact might be different and better during exercise, when the septostomy could be functioning as a “safety pop-off valve.” This concept of better function in patients having an ASD during exercise in the setting of RV hypertension was demonstrated by Austen many years ago,¹⁰ and may in part explain the improvement in exercise tolerance reported by patients in some series.¹⁴,³⁰-³²

With regard to the long-term effects on RV function after septostomy, information is scarce, but there appears to be sustained improvement. Kerstein¹³ and Law³³ have shown improvement in long-term hemodynamics: approximately 2 years after septostomy. Likewise, Espinola-Zavaleta³⁴ showed that, 3 to 6 months after septostomy, there was a decrease in right atrial area and in end-systolic and end-diastolic RV areas, a finding compatible with decompression of the right-sided chambers. In agreement with this decompression phenomenon and the relief of failure is the report from O’Byrne et al,³⁵ demonstrating a significant decrease in b-type natriuretic peptide (BNP) after septostomy. Atrial septostomy may also have additional beneficial effects on RV function. Ciarka and coworkers³⁶ showed a significant decrease in muscle sympathetic nerve activity after the procedure; of interest, sympathetic overdrive in PAH may be one mechanism involved in RVF.³⁷

Spontaneous closure of the septostomy is not an infrequent finding during follow-up. This situation can be overcome by repeating the procedure.¹⁴ In addition, alternative interventions such as deployment of a fenestrated device (ie, Amplatzer septal occluder),³⁸-⁴² concomitant use of a butterfly stent (flared at both extremes),³²,³⁴,⁴³ and cryo-ablation of the septostomy borders¹⁸ have been described. However, the safety and long-term efficacy of these additional interventions remains to be determined.

There is no definitive answer regarding the optimal size of the defect, and the size of the septostomy should be performed on an individual basis. One should aim to increase cardiac output and decompress the RV, but refractory hypoxemia should be avoided. Based on recent experimental data, it would appear that increasing cardiac output no more than 15% to 20% from baseline would provide the greatest benefits and results.⁴⁵-⁴⁷

Although atrial septostomy improves hemodynamic variables that correlate with clinical improvement and survival, true impact of septostomy on survival of patients with PAH is difficult to assess due to lack of controlled long-term studies (something that is also true for most of the current pharmacological
options). However, the survival rates for patients with long-term follow-up in different case series appear to be better when compared with either historical controls or predicted survival. Unfortunately, during follow-up there is a significant drop of cumulative survival in time, reflecting the palliative nature of the procedure. In other words, atrial septostomy does not cure or reverse PAH and the beneficial effects of the procedure erode over time. The short- or median-term impact on survival, however, provides valuable time for the application of other noteworthy interventions (ie, PAH-specific drugs and/or transplantation).

In summary, based on the review of the worldwide collective experience, atrial septostomy stands as an additional strategy in the treatment of severe RVF from PAH. In the majority of cases, the procedure has been performed at an advanced stage of the disease in patients already burdened with a significantly higher risk of death; yet, despite progression of disease in these patients, BDAS frequently leads to clinical and hemodynamic improvement. Analysis of the worldwide clinical experience suggests that procedure-related mortality is decreasing. In this regard, the following guidelines are important: 1) do not perform septostomy in moribund patients (those with RAP > 20 mm Hg); 2) always perform BDAS using a step-by-step approach; 3) employ constant monitoring of hemodynamic variables (RAP, LVEDP, CI, and SaO2); 4) limit the size of the defect to aim for a decrease in baseline SaO2 of no more than 10% and an increase in baseline CI of no more than 15% to 20%; 5) BDAS should only be performed in centers widely experienced in both interventional cardiology and PH. The “ideal” candidate for the procedure remains a patient in functional class III, with RAP between 10 and 18 mm Hg and a baseline SaO2 > 90%, with history of syncope or persistent RVF despite maximal medical therapy as part of a goal-oriented strategy. The procedure may also be considered either as a bridge to lung transplant or as the sole treatment modality when other therapeutic options are not available.

**POTTS SHUNT**

Potts’ aortopulmonary anastomosis was originally intended as a form of palliative treatment for some CHD with diminished pulmonary blood flow. The procedure, which employs a side-by-side anastomosis between the left pulmonary artery and the descending aorta, has been recently reexamined in the management of refractory PAH as a surgical/interventional alternative to atrial septostomy. It shares the same concept and rationale: that is, to produce a right-to-left shunt to increase systemic output, but at a post-tricuspid level, similar to that observed in patients with patent ductus arteriosus (PDA) and PH who survive longer and have less right heart failure than patients with IPAH. In theory, the main advantage of a Potts shunt over an atrial septostomy is that it creates a permanent postcardiac right-to-left shunt that does not lead to arterial oxygen desaturation in the upper part of the body, including the brain and the coronary circulation. Since the original description by Blanc and coworkers of successful application of this surgical procedure in 2 boys with suprasystemic PH after an arterial switch for transposition of the great arteries (Figure 2), experience and interest have rapidly expanded. The surgical procedure is performed under general anesthesia, usually via a left thoracotomy without cardiopulmonary bypass, and the size of the shunt (which remains controversial) is set at ~9 mm.

Until now, this surgical approach has been performed mostly in children with refractory PAH at an advanced stage of disease where Potts anastomosis may be considered a lifesaving procedure. This procedure often results in significant improvement in functional class, exercise tolerance, and reduced levels of natriuretic peptides in survivors. However, there is also an inherent risk of mortality during or after this surgical procedure in this very sick PAH population. Also, adults with PAH and severe RVF undergoing this intervention might have a different postoperative prognosis and higher perioperative mortality.

**TRANSCATHETER POTTS SHUNT**

To bypass the potential risks associated with surgery and after demonstrating its feasibility in animal models, an inno-
ative technique using a transcatheter approach to create a Potts shunt (TPS) has been recently described in humans with PAH. In this report, 4 patients with severe PAH underwent TPS. Under general anesthesia, vascular perforation was guided by fluoroscopy, and the shunt was created via placement of an iCAST 7x22 mm covered stent (Atrium Medical, Hudson, NH, USA) between the left pulmonary artery and the descending aorta. Although considered technically successful in 3 cases, 1 patient died during the procedure as a result of uncontrolled hemothorax, and another died just a few days later as a result of ventilation-associated pneumonia. The remaining 2 patients showed significant symptomatic improvement and had no complications after 4 and 10 months during follow-up.

Baruteau and coworkers have recently published a compendium of their experience with both surgical anastomosis and TPS in the management of PAH. Their pooled data on 24 children (aged 1.5–17 years) who underwent Potts shunt (19 surgical, 5 TPS) for drug-refractory PAH demonstrated severe postoperative complications occurring in 6 patients (25% of the surgical group), including 3 early deaths (12.5%) due to low cardiac output. After a median follow-up of 2.1 years, none of the patients experienced syncope or worsening RVF. BNP/NT-proBNP levels returned to normal in all patients. The authors concluded that creation of a palliative Potts shunt prolonged survival and dramatically and consistently improved functional class in children with severe, drug-refractory PAH.

Bleeding (massive hemothorax) is the most feared complication of TPS. In this regard, computed tomography of the thorax prior to the procedure could help select the ideal candidate for surgery. In this study, the authors described 2 types of relationships between left lower pulmonary artery and descending aorta; in type 1, there is practically no distance between the vessels, and in type 2 the gap between the structures is greater, thus increasing the risk of bleeding. In theory, type 1 patients represent the ideal candidates for TPS anastomosis. A radiofrequency-assisted perforation approach is yet another refinement to try to improve the safety and efficacy of TPS creation.

The concept of the potential benefit of this type of pulmonary-to-systemic shunt in the setting of PH has been applied to the pediatric population by creation of a “functional” Potts by stenting the ductus arteriosus in newborns and infants with suprasystemic PH of various etiologies.

Although creating a post-tricuspid shunt would be intuitive based on data from Eisenmenger patients with PDA, it remains to be determined whether a post-tricuspid defect will prove equal to or superior to atrial septostomy. Apart from the expected reduction in RV afterload, there are several issues to consider when bypassing the pulmonary artery flow to the descending aorta. The most important is the potential equalization of systemic and pulmonary pressures, limiting the ability to further unload the RV and the concern of a left-to-right shunt during exercise and/or the development of systemic hypertension with aging. To address this potential problem, a unidirectional valved conduit for surgical Potts shunt has been developed and tested in an experimental animal model of PAH.

In sum, it appears that Potts anastomosis (surgical or interventional) is indeed an innovative approach for management of PAH and an alternative to atrial septostomy. However, more experience and refinement of the technique is needed both to reduce the risks associated with the surgical approach and to establish TPS as an accepted therapeutic modality for advanced PAH.

CONCLUSION

Despite advances in pharmacologic treatment, PAH remains a fatal disease. BDAS and the recently adopted surgical/interventional Potts anastomosis stand as therapeutic alternatives in selected patients with refractory RVF from PAH. These interventions may improve quality of life and prolong survival in this population. Substantial experience with these procedures has been limited by the relative success of current pharmacologic strategies and the lack of significant expertise to master the techniques; however, these interventions should be available and performed in centers experienced in both interventional cardiology and PH. The optimal timing of when to perform either remains a challenge, but we should not be delayed to the point of being contraindicated or ineffective.

References


Pulmonary Hypertension and Palliative Care: What, When, Where, and Why?

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Summary: Pulmonary hypertension (PH) can be associated with a high level of symptom burden from the disease as well as its treatment. Involvement of palliative care (PC) services may help facilitate discussion regarding goals of care, prognostic planning, and treatment options focused on improving quality of life (QOL).

Background: PC is active total care of a patient whose disease is not fully responsive to curative therapies, with symptom control as the top priority. After a life-limiting diagnosis is made, health care teams and patients determine prognosis, whether cure is attainable or reasonable, what treatment options are available, risks and benefits of associated treatments, and how treatment or nontreatment will impact QOL and survival. QOL is often the focus of palliative interventions, with the goal to minimize symptoms and empower patients with accurate information to help affirm life and meet objectives of care.

Implications for clinicians: PC can begin at the onset of symptoms in a disease that cannot be cured. Early PC may help facilitate discussion regarding goals of care when patient expectations are discordant with prognosis. While PC is a responsibility of all clinicians, subspecialist assistance can be helpful when a clinical decline occurs, in the setting of uncertainty, when patients are removed from the transplant list, or when long-term QOL issues are present.

Conclusion: Communication with patients who have PH can be delicate and requires an understanding of the disease’s process, trajectory, and prognosis. PC teams possess communication skills that may benefit patients and providers with QOL optimization, delivery of difficult news, advanced care planning, and shared decision-making.

Pulmonary hypertension (PH) involves progressive remodeling of the pulmonary vasculature, resulting in elevated pulmonary artery pressure, right ventricular failure, and death. PH is classified into 5 groups depending on etiology and hemodynamic parameters, which impact prognosis and treatment options. PH’s negative impact on quality of life (QOL) is well-documented, with common symptoms including fatigue, overall decline in physical and emotional wellbeing, pain, dyspnea at rest or exertion, chest discomfort, lower-extremity edema, abdominal bloating, and early satiety. With the advent of PH-directed medications, median survival has improved from 2.8 years to more than 7 years.

Symptoms can occur in the setting of progressive PH, as well as from PH-directed treatment. In a study of over 300 patients with PH, the majority of patients (69%) noted significant rest or exertional dyspnea or fatigue as a major symptom, while also reporting fatigue (39%), pain (35%), and depression (32%). A patient’s QOL also can affect primary caregivers including spouses, children, and friends. Despite these challenges, only 8% of patients in a multicenter survey considered palliative care (PC) involvement as an option, and only 1.4% of patients have actually seen PC clinicians as regular providers within their multidisciplinary care team.

Palliative care is the active total care of the patient whose disease is not fully responsive to curative therapies, with symptom control as the top priority. PC focuses on anticipation, prevention, and treatment of symptoms or suffering, with improvement in QOL as a center point of care. Efforts with PC should empower patients by affirming life, but also in recognizing that sometimes death is inevitable. Despite being mentioned as a concern by patients with PH and their providers, no specific therapies are excluded from a PC plan of care.

Over the past 2 decades, the palliative paradigm has shifted toward establishment of a comprehensive management program by multidisciplinary teams that are involved before the end of life. PC is more comprehensive than hospice care, and is recommended to begin when pervasive symptoms and QOL issues exist in the setting of an incurable, life-limiting illness.

Hospice care is a specific subset of PC with the distinction of providing supportive care to patients who have a terminal illness with limited life expectancy of less than 6 months if the disease follows its anticipated course (Figure 1). Hospice care is a Medicare or private insurance benefit in which care is also provided by an interdisciplinary team, most often in patients’ homes. Care is directed at maximizing comfort, dignity,
and QOL as patients approach the end of life. Patients receiving hospice care are typically no longer receiving disease-modifying treatments, notably, because hospice reimbursement is capitated on a per diem basis. The reimbursement must cover the entirety of patients' care related to the hospice diagnosis, including but not limited to durable medical equipment, medications, and nursing care. This model presently reimburses an average of $160 per day (noting some geographic variability). When viewed in this manner, it becomes clearer why certain disease-directed medications such as parenteral prostaglandins and oral vasodilators such as endothelin receptor antagonists (ERAs) or phosphodiesterase type 5 (PDE-5) inhibitors may be cost prohibitive for some hospices (Table 1).

**WHY PC AND WHAT CAN IT ADD TO THE PLAN OF CARE?**

Critical initial steps are to address patient expectations and establish goals of care that are important to the patient and caregiver(s). After a serious or life-limiting diagnosis is made, health care teams and patients often need to determine prognosis, understand whether or not cure is attainable or reasonable, what treatment options are available and what the risks/benefits of these treatments are, and how treatment or nontreatment will impact QOL and survival. PC providers often focus less on being “negative” about the prognosis, rather, they strive to ensure that patients receive realistic and hopeful information to make the best possible choices. PC models continue to evolve with the most up-to-date schema, depicting PC initiation early in the disease process with increasing inclusion as the disease progresses, rather than late integration once conventional medical therapy has failed to arrest disease progression or suboptimally treat symptoms and disease (Figure 2). PC's primary focus is on symptom control while empowering the patient and his/her caregiver to live as well as he/she can for as long as possible. Early incorporation of PC may help facilitate discussion regarding goals of care when patient expectations are discordant with prognosis. Namely, PC consultation has

**Table 1. Differentiating Palliative Care From Hospice From Comfort Care in PH.**

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<th>Care</th>
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<th>Primary Focuses of Care</th>
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<th>Delivered by</th>
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</thead>
<tbody>
<tr>
<td>Palliative Care</td>
<td>Longitudinal or episodic Can begin with the onset of serious, life-limiting illness</td>
<td>Symptom management Quality of life Delineating goals of care Supporting families and caregivers</td>
<td>Reimbursement is analogous to other subspecialty consultation (ie, infectious disease, cardiology)</td>
<td>Clinician who is delivering primarily, or by a subspecialist who may have support of an interdisciplinary team</td>
</tr>
<tr>
<td>Hospice Care</td>
<td>Approaching end of life Generally begins when life expectancy is less than 6 months, if the disease runs its expected course</td>
<td>Team-based support services To support patients, families, and caregivers Aggressive symptom management Where comfort and quality of life are major primary goals Bereavement and volunteer support</td>
<td>Can be Medicare or from private insurers often modeling after Medicare model Limited per diem stipend (~$200/day) for all care related to hospice diagnosis Use of costly medications may be restricted</td>
<td>Hospice agency involved, which may be overseeing care, or may be collaborating with a primary physician or specialist care team</td>
</tr>
<tr>
<td>Comfort Care Only</td>
<td>Very end of life Generally begins in final hours or days, in hospital or home Starts when all treatments that are not focused on comfort are discontinued</td>
<td>Focus is purely on comfort of the patient Medications that are not contributing to comfort are discontinued Opioids, anxiolytics, and sedatives are used in an appropriate fashion to maximize comfort Not ALL medications should be stopped if they can help the patient to achieve their goals of care</td>
<td>Variable Depends on whether or not a patient is hospitalized, in a facility, or at home Depends on whether or not hospice care has been elected</td>
<td>Variable Depends on whether or not a patient is hospitalized, in a facility, or at home Depends on whether or not hospice care has been elected Depends on specific care needs</td>
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behave been shown to facilitate the honing of advance directives into preparedness plans, addressing end-of-life scenarios more common in a particular disease process.\textsuperscript{11}

Historically, most patients with PH express wishes to die in the comfort of their home surrounded by their loved ones. Yet, two-thirds of such patients die in a hospital setting. In one study of patients with PH, more than 80\% of in-hospital deaths occurred in the intensive care unit (ICU).\textsuperscript{12} Importantly, disease-directed PH medications or associated hospital policies (such as requiring a patient to be in the ICU or a monitored bed) may influence these outcomes. Limited data exist regarding end-of-life experiences of patients with PH; however, in one study, caregiver knowledge about PC and hospice services was noted to be less than that of life-support options.\textsuperscript{12} It is critical for patients and families to understand all alternatives available to them in the setting of advanced illness, to allow for empowered and informed choices honoring patients’ goals, preferences, and values approaching the end of life.

QOL AND SYMPTOM BURDEN IN PH

Palliative care involvement may be appropriate to begin at the time of diagnosis, even if prognosis is not established. In the setting of pulmonary arterial hypertension (PAH) or PH due to other etiologies, PC management can assist with symptom burden and QOL at any point, help when a clinical decline occurs or when patients are removed from the transplant list, or can support long-term comanagement. The heavy and often complex symptom burden in patients with PH/PAH can represent a management challenge, and can be a major source of negative impact on QOL for patients and their primary caregivers. In a recent survey, physicians with experience treating patients with PAH noted they most frequently encountered patients with exertional dyspnea, fatigue, edema, depression, and anxiety, and described high self-reported comfort levels in addressing PH-specific medications to improve these symptoms. However, the same physicians reported less confidence in addressing pain management, depression, and other QOL issues, suggesting a role for PC.\textsuperscript{8}

While not always related to a need for PC, many patients with PH mention feeling isolated and experiencing feelings of insecurity, and note their disease impacts their physical health and activity as well as their mental health, social functioning, and emotional well-being.\textsuperscript{13} Health-related QOL surveys have shown that patients with PAH describe symptom burden on par with the severely reduced QOL reported in patients with chronic obstructive pulmonary disease and renal failure, and treatment-resistant cancer.\textsuperscript{14} A common challenge is that for many of these patients, traditional hemodynamic parameters (aside from right atrial pressure) often fail to correlate with impaired QOL in the setting of PAH.\textsuperscript{15}

Patients with PH frequently mention symptoms including fatigue, exertional dyspnea, and sleep difficulty,\textsuperscript{2} and con-

Comitant psychiatric disorders are also commonly described and affect up to 35\% of patients with PH.\textsuperscript{16} Tools to assess patient-reported outcomes may be helpful in determining the QOL-related issues. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) was developed to measure patient-reported outcomes in 3 domains: symptoms, functioning, and QOL, and it has been used in PH populations as well as other inventories such as the SF-36 (short form).\textsuperscript{17} Patients’ CAMPHOR scores have been shown to correlate well with SF-36 scores, as well as 6-minute walk test (6MWT) distance.\textsuperscript{18}

Many of the treatment options for PAH require extensive planning and adherence to daily routines, which can be challenging, but these drugs also result in variable side effects requiring further adjustments to daily plans. For example, PDE-5 inhibitors may result in gastroesophageal reflux, jaw pain, skin flushing, and headaches.\textsuperscript{19} ERAs may result in nasopharyngitis/nasal congestion, headache, anemia, liver failure, and lower extremity edema.\textsuperscript{20,21} Prostacyclin analogues often result in skin flushing/hot flashes, nausea, headache, peripheral neuropathy, and diarrhea as well as complications from central intravenous catheters for parenteral therapy.\textsuperscript{22} Soluble guanylate cyclase stimulators may cause headache, skin flushing, hot flashes, systemic hypotension, and syncope.

Historically, PC involvement occurs near the end of life in the setting of severe symptomatic right heart failure refractory to optimal medical management, often after initiation of dual or triple therapy. Despite frequent visits and improved disease/symptom awareness with earlier diagnosis and many treatment options, symptom burden remains high and incorporation of PC may assist in improvement of QOL. The level of support can be tailored to the clinical situation. However, PC involvement historically occurs in the minority because of perceptions that the patient was doing well or was “not sick enough” for PC, or the topic was not broached by their primary provider.\textsuperscript{1} Of 76 experienced physicians who treat

![Figure 2: Care across a patient’s life span. Though seen here as linear, the course for patients with PH is often marked by periods of exacerbation and relative stability.\textsuperscript{36} Modified from the World Health Organization. EOLC=end-of-life care; ICP=integrated care pathway.](image-url)
PAH patients, most affirmed major PAH symptoms and expressed high comfort levels with treating symptoms and discussing end-of-life care plans with patients and family. Yet, only 43% of physicians reported a comfort level in assessing QOL and less so indicated confidence managing QOL issues. The majority of surveyed physicians requested PC consultation within the last 12 months, most commonly for end-of-life care/active dying (59%), hospice referral (46%), comanagement of dyspnea, or impaired QOL (40%) (Table 2). Barriers to PC consultation include patient non-approval (51%) and the perception of “giving up” by the patient (43%), and 36% of providers felt comfortable addressing symptom management, QOL, and end-of-life care without need to include PC (Table 3). When PH physicians were surveyed about therapeutic options for a case vignette describing an ill PAH patient with functional class IV symptoms/end-stage PH on combination therapy and intolerant to prostacyclin analog with 6 to 12 months of prognosis, most respondents recommended initiation of oxygen and diuretic escalation (Figure 3). Approximately half of respondents recommended a clinical trial (51%), while 49% considered higher-risk invasive intervention of atrial septostomy. Despite a poor prognosis and evidence of treatment failure, only 40% of polled physicians considered PC consultation and only 12% weighed hospice as an appropriate option. The results highlight the historical perceived role of PC in the PH medical community and emphasize a growth opportunity.

WHY: COMMUNICATING AND PROGNOSTICATING IN PH WITH UNCERTAINTY
Communication with patients who have PH requires preparation and a knowledge base of the underlying disease process, disease trajectory, and prognosis. These communications may arise from the primary PAH treatment team or may come from different parts of the multidisciplinary team depending on comfort level and expertise. Collaboration with PC may be initiated with an intensive up-front assessment at the time of diagnosis, with long-term follow-up on an as-needed basis when symptoms or side effects occur, or may be initiated only when symptoms/side effects begin to outweigh the derived benefit from PH-directed therapies. How do we measure successful or beneficial PC interventions? Quality metrics in palliative care may be best measured by QOL rather than length of survival as a surrogate marker. The ultimate goal of PC is a patient-centered focus with a plan that aligns with the patient’s value system and provides a supportive structure to uphold those values and improve QOL. Despite historical obstacles, implementation of PC may improve QOL and provide a respite from symptoms and medication side effects while neither hastening nor postponing death.

Palliative care consultation can play an important role in the care of patients with refractory symptoms in PH. Dyspnea in particular can be an especially burdensome and frightening symptom, and breathlessness may persist and progress despite maximal disease-directed interventions. The primary treatment of dyspnea is to address the underlying cause; however, it is important to conceptualize all of the potential factors that may play a role in dyspnea when managing a patient with subjective breathlessness. “Total dyspnea” refers to the multitude of physiologic, psychological, social, and existential influences on a patient’s sense of dyspnea. Opioids have been shown to be both effective and safe in the treatment of subjective dyspnea; however, providers often cite a lack of experience in their use and concerns about legal and physiologic consequences as barriers to their use. PC teams have expertise in advanced symptom management and may be beneficial for patients with a high symptom burden, particularly in the setting of refractory dyspnea.

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for patients with PAH. These interventions may include but are not limited to invasive and noninvasive testing, PH-directed medication up- or down-titration, and implementation of a PC plan. Benza et al. provided a framework for predicting outcome in patients with PAH through the REVEAL risk score calculator, which utilizes hemodynamic information, clinical information, and epidemiologic data readily available in most patients. The score allows risk stratification of PAH patients and outlines certain high-risk features such as connective tissue disease-associated–PAH, portopulmonary hypertension, hypotension, tachycardia, elevated mean right atrial pressure, pericardial effusion, and 6MWT distance among other variables. Prognostication that identifies a patient at high risk of morbidity or mortality may provide a valuable opportunity to implement PC at a point that can positively impact QOL rather than delaying involvement until end of life. Research trials in PAH recently have had a shift toward hard endpoints such as time to “clinical worsening,” defined as functional class worsening, initiation of a parenteral prostacyclin agonist, hospitalization, transplant, atrial septostomy, or death rather than relying predominantly on a change in 6MWT distance. The REVEAL risk score accurately predicts 1-, 2-, and 5-year survival to assist clinicians in detecting those at high risk for not only clinical events such as hospitalization but also overall poor prognosis. For example, 1-year survival in 3001 PAH patients with “clinical worsening” was 78% vs 94% in patients who did not meet criteria for clinical worsening (Figure 1). The pattern was similar in newly diagnosed patients as well as in patients with a previous diagnosis. Disease trajectory appeared to accelerate most in the 4 to 6 months after a hospitalization. 6MWT distance has long been used by clinicians as a simple measure of functional capacity in patients with PAH. The distance is part of the REVEAL risk calculator with overall cutoff values of >440 m or <165 m, imposing a positive or negative prognostic indication respectively. Farber and colleagues recently illustrated the prognostic ability of 6MWT distance deterioration on serial measurement to reflect worsening prognosis and demonstrated that stable or improved walk distance had no change on survival.

Recently, REVEAL investigators demonstrated utility of the REVEAL risk score calculator at serial assessment, highlighting that risk score changes have prognostic implications. Only 38% of patients (n=959) had no change in risk score, while 32% had an improvement and 30% had a worsening in score. The 1-year survival for patients with “decreased score” (improvement in variables) compared to “no change in score” and “increased score” (worsening in variables) was 94%, 90%, and 85% respectively. Increased risk score by even 1 point (worsened score) carried with it a hazard ratio of 1.67, while score improvement equated a hazard ratio of 0.57 when adjusting for risk at enrollment into the REVEAL registry. Despite advances in medical therapy, improvement in long-term survival remains low at 61% to 65%. Change in REVEAL risk score or worsening in 6MWT distance on serial evaluation reflects a change in disease trajectory and may provide an important opportunity to not only modify medical therapy but also explore initiation of PC to assist in symptom attenuation and QOL improvement.

Communication about disease process, trajectory, and prognosis may be challenging and riddled with significant uncertainty as providers are often dealt the difficult task of extrapolating population-level estimates to an individual patient with innumerable potential confounders. With a goal of truthful, honest discussions about prognosis, providers may face concurrent fears about taking away patients’ hope and concerns about lack of training or appropriate time for these discussions. Three central tasks have been described when approaching uncertainty with patients and families: to normalize uncertainty, address the associated emotions, and help manage the effects of the uncertainty. Shared decision-making has been highlighted by the American Heart Association and seeks to have providers and patients work together to make important treatment decisions in the context of a patient’s preferences and values in an iterative manner. PC teams possess advanced communication skills that may benefit the patient and providers in the processes of delivering difficult news, performing advance care planning, and making shared decisions.

References


Pulmonary Hypertension Patient Navigation: Avoiding the Perfect Storm

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Pulmonary arterial hypertension (PAH) is a progressive, incurable disease that presents a challenging journey for all involved. Specialized, complex care and treatment is needed for this population of patients, and should be provided in an organized, systematic manner to promote optimal patient outcomes. The concept of patient navigation can be used as a framework for the pulmonary hypertension (PH) center, so that care delivery is well structured and PAH patients have a guide to assist them through all aspects of the health care continuum. This article will focus on how a PH patient navigation program can be implemented and the role of a PH nurse navigator, using the Christiana Care Health System Pulmonary Hypertension Program in Newark, Delaware, as an example. There have been many advances in PAH diagnosis and treatment in the last 20 years, and the time has come to introduce a PH patient navigation model that can be used as a guide to structure PH programs.

PATIENT NAVIGATION
BACKGROUND
The multidisciplinary team approach to caring for pulmonary arterial hypertension (PAH) patients has been documented as the accepted standard of care, and patients benefit from other disciplines that may be involved in the treatment plan in addition to doctors and nurses such as nurse practitioners, pharmacists, respiratory therapists, and social workers.1 There can be many obstacles to proper PAH treatment that must be overcome by the pulmonary hypertension (PH) team to better control symptoms and achieve a longer life span for the patient. The path is not always clear, and there is often a great deal of time and energy expended to navigate the maze of all that is necessary to achieve effective management of the disease, especially for patients and their caregivers.

A growing number of resources are available to assist the PH team with different aspects of PAH care and treatment, but none that includes a model of all care components the PH center can use to help structure a planned or existing PH program. A PH patient navigation model includes principles for the PAH patient population that can be adopted by the center to enhance multidisciplinary efforts toward individualized treatment goals. The concept of patient navigation was founded in 1990, by Dr. Harold P. Freeman in Harlem, New York, to focus on health care disparities and effectively manage cancer patients across the health care continuum by using professionals to support individual patients.2 Today, the Harold P. Freeman Patient Navigation Institute trains individuals to become patient navigators not only for cancer patients, but also for other chronic illnesses, and his program is the gold standard of patient navigation.3 Trained patient navigators are better equipped to assist patients with barriers to care because there are well-defined roles and responsibilities and a set model to follow. Many cancer centers, such as the one at Christiana Care Health System (CHHS), use patient navigation to achieve better outcomes, increase patient satisfaction, and decrease institutional financial burdens by expanding timely access to care. Since 2015, all cancer programs accredited by the Commission on Cancer must have patient navigation as the standard of care.2,4 Thus, PAH patients can likewise benefit from the consolidated efforts that a PAH patient navigation model can bring to overall care and treatment.

INCORPORATION OF PATIENT NAVIGATION INTO THE PH PROGRAM
The PH program at CHHS has the opportunity to incorporate patient navigation principles into the way patients are managed, using an adaptation of the Harold P. Freeman Institute’s philosophies. In the model developed for the CCHS PH program, the basic continuum spans the period between diagnosing a patient with PAH through optimal symptom management and prolongation of lifespan (Figure 1). The overall goal of the model is access to PAH diagnosis and treatment, as statistics show that the average time between symptom manifestation and treatment remains at 2.8 years, and precious time is lost until the diagnosis is made.5 Therefore, the first area of the model covers early recognition of patients at higher risk for developing PAH. Patients that are diagnosed at earlier stages and receive intervention have been proven to have decreased disease progression.6 Although not uniformly accepted by the medical community, according to screening guidelines from the American College of Cardiology Foundation and the American Heart Association, patients with known familial PAH and/or BMPR2 mutations, systemic sclerosis,
HIV, portal hypertension, recent acute pulmonary embolus, congenital heart disease with shunt, sickle cell disease, and prior use of appetite suppressants warrant periodic screening for PAH. Medical professionals are likely to see patients with these conditions that have symptoms of unexplained dyspnea, syncope, and lower-extremity edema that could be PAH, so these patients would benefit from definitive testing by a PAH specialist to rule out the disease. Outpatient stays. The PH team must communicate test findings and treatment plans to all practitioners involved with the patient so that care is a seamless, timely, collaborative effort.

ROLE OF THE PH NURSE NAVIGATOR
While there may be patient navigators in other chronic care programs that are not nurses, a nurse in the role of the PH program navigator is most suitable. The PH nurse navigator is a pivotal team member that can serve as the triage person for the PH team and coordinate all patient care activities once the PAH diagnosis is made. This nurse should obtain a comprehensive patient assessment at the initiation of treatment, and these activities remain at the forefront of patient navigation. Key information regarding patient support systems can be gathered at this time so that any barriers to PAH treatment can be identified and addressed from the start. The PH nurse navigator gathers information regarding drug enrollments for PAH medications (which are all very expensive) and obtains necessary prior authorizations. An essential skill for this nurse is experience in drafting appeal letters to insurance companies with the physician that include clinical studies in support of the drug’s medical necessity, as some insurance companies will deny increased doses of certain medications or some treatments altogether. The PH nurse navigator also provides education about PAH medication along with providers, pharmacists, and specialty pharmacies. Patients should be given information on copay assistance programs to help them obtain the prescribed drugs and any other resources that they may need. The nurse navigator position is crucial to the team as a whole because this is where the responsibility for patient navigation lies. The nurse navigator assists with patient care throughout the process, including all inpatient and outpatient services, and is the liaison between care settings so that vital information regarding the PAH treatment plan is not lost as the patient transitions from one setting to another. The relationship of the PH team with inpatient providers and nursing staff requires regular communications to ensure that all are addressing common treatment goals for the patient. The PH nurse navigator role confirms this care association via face-to-face meetings, telephone calls, or exchange of office notes and discharge summaries from inpatient stays. The PH team must create a notification mechanism when a patient is admitted to the hospital.
PAH therapies to ensure up-to-date dosing is ordered.

Besides the array of medication currently available to treat PAH, patients should still be considered for lung transplantation evaluation based on prognosis and response to prostanoid therapy. An established relationship with area facilities should exist if the PH center does not have lung transplantation available at its facility. Also, patients with chronic thromboembolic pulmonary hypertension (CTEPH) should be referred to facilities that can evaluate for a pulmonary thromboendarterectomy, as this surgery has been shown to improve hemodynamics and survival in these patients.

SUPPORT SERVICES AND END-OF-LIFE CARE

The care of PAH patients involves much more than prescribing medications and treatments, and most patients require access to support such as financial, social, and logistical services. Resource information should be readily available for patients so treatment obstacles can be overcome if possible. Barriers to PAH treatment including lack of insurance, patient education level, logistics of transportation, inability to work, gaps in language skills, and other cultural issues can make it difficult for the patient to navigate health care systems and receive adequate care. Many PAH patients need guidance on how to apply for disability; others require assistance in applying for medical transportation to come to appointments; and some have social concerns that must be addressed. Issues related to a patient’s inability to comprehend a complex drug regimen, lack of housing, or poor family support can greatly affect the PAH treatment plan, and the PH team must be prepared to assist patients in dealing with these matters. Having a social worker or financial counselor as part of the PH team offers valuable assistance for patients in these areas. In addition, anxiety and depression are common comorbidities in PAH patients associated with the debilitating symptoms and drastic lifestyle changes that arise as the disease progresses. Consequently, PH centers should have the ability to provide mental health services or a mechanism to refer patients to outside resources. Every PH center should provide access to a PH support group or deliver information regarding area support groups associated with the Pulmonary Hypertension Association (PHA), including the PHA telephone support group if the patient cannot attend in person. Patients and caregivers alike should be encouraged to join a support group for education, encouragement, and communication with other patients—all of which may help patients gain skills to cope with PAH. PHA offers a considerable amount of resources in all of these areas for patients, caregivers, and providers.

Since PAH is an incurable disease that is progressive and often fatal, the PH team must be prepared to assist patients and caregivers with living with a chronic illness, in addition to facilitating end-of-life discussions and decisions. The PAH specialist should introduce the recommendation for palliative care as an adjunct to symptom control and enhancement of the patient’s quality of life when appropriate. If all treatment efforts have been exhausted, hospice services should be offered, and the PH team must support the patient and family through this experience. The nurse navigator role is particularly important to assist patients in identifying palliative care or hospice programs that will fit their needs. PAH patients that elect hospice usually have to terminate prostacyclin or other therapies due to the cost of medication, unless there is another terminal diagnosis other than PAH. PAH medications and treatments are considered aggressive therapies and are in contrast with hospice concepts and criteria, so they are not covered by insurance.

PATIENT SELF-NAVIGATION

Most importantly, a climate supporting patient self-navigation is essential within the PH model to ensure patients are empowered to be involved in their own care and treatment decisions as much as possible. Through the development of the patient-care team relationship, the patient’s attitude and understanding of PAH should be determined, along with adherence to treatment directions and testing, and awareness of when to reach out to the PH practitioner with questions or concerns. The PH nurse navigator can triage patients’ needs and work with them on an individual basis to offer suggestions for tools to help them stay organized with treatment and progress, such as weight charts, fluid management guides, and symptom diaries. Patients should be encouraged to participate in treatment decisions, and self-efficacy must be fostered as treatment progresses.

CCHS PH PROGRAM

During the process of establishing a PH patient navigation program, the PH team at CCHS has experienced many changes in the way PAH patients are cared for. The CCHS program sees approximately 90 adult PAH patients, and the hospital has a separate heart failure clinic. All diagnostic testing is provided at CCHS, as well as all forms of PAH treatment: oral, inhaled, subcutaneous (SQ), and intravenous (IV) therapies. There is a dedicated outpatient clinic within the hospital, and patients are cared for and treated by the same team members whether they are inpatient or outpatient. PAH patients are referred to outside facilities for evaluation for lung transplant or pulmonary thromboendarterectomy as applicable.

The CCHS PH program was established in the late 1990s with Dr Gerald O’Brien, a physician who was board certified in pulmonary disease and critical care and had been a PAH specialist for 20 years. There was also a nurse clinical specialist, a clinical pharmacy specialist, and a few staff nurses on the pulmonary step-down unit. Today there is a full team with the addition of a nurse practitioner, nurse navigator, and research nurse. The present medical director is Dr Jeffrey Stewart, who is board certified in pulmonary disease, critical care, and internal medicine. Social work services are available on an as-needed basis from the pulmonary step-down unit. The PH team provides after-hours coverage for patients, and there is a pager notification system in place when one of the IV/SQ/inhaled therapy patients is seen in the emergency department (ED). All patients on IV/SQ or inhaled therapy
are admitted to one unit where the nurses have ongoing, specialized training. The intensive care unit nurses are also trained, and there is a PAH patient algorithm for the ED nurses to follow. The PH team meets every month to discuss all aspects of the program and is continuously developing new systems to enhance patient care. The team has also worked diligently in educating staff at the hospital and within the community. A quarterly PH support group meeting is held at the hospital, and patients are offered the opportunity for inclusion in clinical trials through the PH program. A patient navigation assessment tool is used to help identify areas of patient concern and barriers to PAH treatment and care. There is access to a dietitian and mental health professionals within the CCHS hospital system, and reporting tools are being developed to assess program quality. The presence of a central PH nurse navigator has been an important feature in decreasing fragmentation of care, and patient satisfaction has been enhanced in the CCHS program by anecdotal information from patients and caregivers.

Instituting a patient navigation system can support those responsible for taking care of PAH patients by providing a springboard from which policies, procedures, and other program attributes can be formulated. PH nurse navigators that have clearly outlined responsibilities and duties can enrich a PH program and streamline care. Patient safety is paramount to every PH program, and there must be systems in place to protect patients from unintended harm that can be caused by health care personnel not trained to care for and treat PAH patients. These patients require the regular support of the PH team to guide them through all aspects of care and treatment, and the PH team needs the type of structure a patient navigation model provides. There is evidence that when patient navigation services are received, patients are more satisfied with care and more likely to adhere to their treatment plan. Therefore, both the PAH patient and the PAH team benefit from the presence of a PH patient navigation model, and the partnership between the two can create a solid foundation for ideal treatment outcomes.

References
Despite remarkable advances in therapy for pulmonary arterial hypertension (PAH), this disease remains life-threatening and incurable, and often has a profoundly negative impact on quality of life. As the illness progresses, common symptoms including fatigue, dyspnea, chest discomfort, and lower-extremity edema may become disabling as PAH is less responsive or refractory to therapy. In this issue of Advances, Fenstad and colleagues provide an outstanding overview of palliative care, including definitions and opportunities for addressing disabling symptoms as a primary goal rather than simply viewing them as indicators of underlying disease stability. These authors also present sobering survey data that indicate only 40% of providers recommended palliative care consultation for a patient with advanced PAH in a clinical vignette, highlighting a potential “growth opportunity.”

The obstacles to achieving this increased utilization of palliative care may include patient fears/possible misunderstanding of the terminology (such as equating palliative care with hospice) and other physician-perceived barriers to palliative care. The discussion that follows considers some practical steps that might be taken in the near term to lower the barriers to palliative care access in patients with PAH, such that the benefits described so well by Fenstad et al. may be better realized. These barriers to improved integration of palliative care with PAH may be loosely classified under 3 headings: those that can be addressed by increased education, those that can improve patient and provider communication, and those that can address access to palliative care services.

EDUCATION TO IMPROVE UNDERSTANDING AND ACCEPTANCE OF PALLIATIVE CARE

Given the challenges surrounding the understanding of palliative care and a suboptimal level of comfort in accessing these specialized services, efforts to educate patients, caregivers, and PAH providers will likely be necessary to achieve a higher level of integration between palliative care and PAH. The patient/caregiver education aspect is often spearheaded by their peers (through PAH support groups) with the support of the Pulmonary Hypertension Association (PHA). PHA recognizes the opportunity to engage patients and caregivers through their established and trusted online presence. PHA’s patient services staff is developing expanded palliative care content to address this area of need.

Engaging physicians in education and/or retraining in palliative care is also key to improving their ability to consider and refer patients for palliative care consultation earlier in their illness trajectory, especially if more aggressive treatment of symptoms is of potential benefit. Multiple online resources have been developed for physician reference (eg, https://getpalliativecare.org/resources/clinicians/, http://www.nhpco.org/resources/end-life-care-resources); however, the improvements necessary for transformational integration of PAH and palliative care may require a systems-level solution. To that end, palliative care advocacy groups including the Center to Advance Palliative Care have proposed opportunities for workforce development that would be best supported by congressional action. These proposals may involve: 1) expanding palliative care centers (addressed in greater detail below), which would take a role in developing palliative care curricula for providers; 2) establishing incentives (eg, research funding) for palliative care team members such as physicians, nurses, social workers, and chaplains to train clinician educators to disseminate palliative care strategies; and 3) reforming medical education to support specialty development in areas such as palliative care. As patients/caregivers and providers progressively gain knowledge and acceptance regarding the value of palliative care, there is potential for a synergistic effect that may result in more PAH patients benefitting from improved symptom control and better quality of life.
IMPROVING PATIENT AND PROVIDER COMMUNICATION

Precise communication of the present functional state of patients with PAH has benefited from use of structured test results, including 6-minute walk distance, World Health Organization functional class, serum brain natriuretic peptide levels, and echocardiographic data. Communication between health care providers, patients, and families regarding experience and impact of daily symptoms in PAH is arguably more challenging than that pertaining to functional capacity. This can hinder the delivery of appropriate palliative care and suggests the need for a formal assessment tool for PAH symptoms.

The gold standard for diagnosing the severity of a symptom is patient self-reporting. However, symptom communication may be imprecise (e.g., “is it better or worse than it was before?”) and may represent an important unmet need in PAH management. The Edmonton Symptom Assessment System (ESAS), as a tool designed to assist in the assessment of symptoms common in a patient with any life-limiting/life-threatening disease, may offer some ability to address this need.

The ESAS provides a clinical profile of symptom severity (rated from 0-10) over time, and provides a context within which symptoms can begin to be understood. However, it is important to remember that it is not a complete symptom assessment in itself and should be used as just one part of a holistic clinical assessment. Repeated assessments may be completed either by the patient alone, by the patient with nursing assistance, or by the patient’s caregivers, at defined intervals until the symptoms are well-controlled. These assessments may occur daily for patients in an institutional care setting (e.g., hospital or subacute rehabilitation center) or perhaps weekly for patients at home. If symptom control is not attained at an acceptable level or consultation about possible care options is needed, patient assessments by palliative care consultants should be considered. The ESAS is, of course, not the only instrument to improve communication regarding symptoms between patients and providers. Hopefully future research will either validate the utility of the ESAS in PAH or provide effective alternative assessment tools.

ACCESS TO PALLIATIVE CARE SERVICES

A 2002 report titled “The Supply, Demand and Use of Palliative Care Physicians in the United States,” prepared for the Bureau of HIV/AIDS, Health Resources and Services Administration, revealed that 64% of American Academy of Palliative and Hospice Medicine-certified physicians felt there was a need for more palliative physicians to meet patient needs. Thus, it is encouraging that palliative care is one of the fastest growing services in modern health care. Since the 2002 report, the number of palliative care teams within US hospitals with 50 or more beds has increased by 157% from 658 in the year 2000 to more than 1692 in 2012. Of hospitals with more than 100 beds, 55% offer a palliative care program, and nearly one-fifth of community hospitals have palliative care programs. Furthermore, over the past 10 years, more than 1000 new hospital-based palliative care programs have been created. While these data reflect overall trends, regional variation in access to palliative care is considerable. The prevalence of palliative care in hospitals is highest in the Northeast and lowest in the South (when considering facilities of all bed sizes); however, the South has the highest prevalence of palliative care programs in hospitals with more than 50 beds.

The major ongoing barriers to offering palliative care at all health care facilities presently seems related to the lack of workforce training programs, inadequate funding for research, and payment models linked to quality measures. The US Department of Veterans Affairs has launched a program to address workforce training with a goal of making palliative care available in all regions and settings. Future funding for research and efforts to establish payment mechanisms based on quality show great promise for the coming years, due to interest in all the key stakeholders. The Center to Advance Palliative Care has proposed specific policy initiatives at the federal level to help convert that promise to a reality. A Palliative Care Provider Directory of Hospitals is available online as a practical resource and may help patients and providers across the United States locate hospitals that provide palliative care. Additional resources available on the www.getpalliativecare.org website identify its value and include basic definitions of palliative care and handouts for patients and families.

In conclusion, a marker of successful integration of palliative care for patients with PAH will be the consideration and implementation of a palliative care consult in a manner similar to, for example, a renal consult. Renal consults are widely accepted by patients and providers: details of the renal illness can generally be communicated in precise terms. These consults are often performed well before end-stage illness, and access to nephrologists is widespread. Palliative care integration in PAH faces challenges to reach a similar state. However, the recent nationwide expansion of palliative care programs, combined with stakeholder interest in increasing research and establishing viable payment models, suggest optimism regarding the future of palliative care integration in the care of patients with PAH.

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Pulmonary Arterial Hypertension: “A Journey to Lung Transplant”

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Presentation: A 31-year-old female presented to her family physician 15 years ago with subtle but gradually worsening dyspnea on exertion (DOE) over the previous 5 years. Prior to these symptoms, she had been very active, running 5 miles a day. She felt her running was now limited by this progressive shortness of breath (SOB). She had no significant medical, social, or family history. Her chest radiograph and initial labs were reportedly unremarkable, and she was told her mild DOE was likely secondary to deconditioning. However, 6 months after her initial visit, her dyspnea had progressed to the point where she was SOB with just walking. She did have one presyncopal episode while attempting to exercise. Her physician referred her to a pulmonologist after the screening electrocardiogram revealed right axis deviation.

Assessment: Pertinent physical findings by her pulmonologist included increased jugular venous distension, a loud P2 on auscultation, clear lung fields, and mild bilateral lower extremity pitting edema. Pulmonary function tests (PFTs) showed mild restriction and a diffusion defect of 66% (Table 1). An echocardiogram (ECHO) showed dilated right-sided chambers, moderately reduced right ventricular (RV) function, and an elevated pulmonary artery systolic pressure (PASP) of 80 mm Hg (Figure 1). A complete evaluation for the causes of pulmonary hypertension (PH) was performed. Liver function tests, complete blood count, renal function, hepatitis panel, HIV, and a full autoimmune workup were found to be normal. A chest computed tomography (CT) with pulmonary embolism (PE) protocol was negative for an acute PE; however, it did show an enlarged pulmonary artery (Figure 2). Lower-extremity Dopplers were negative for any peripheral thrombi, and a ventilation-perfusion (V/Q) scan was negative for chronic thromboembolic PH. A right heart catheterization (RHC) revealed no shunts or other signs of congenital heart defects, but showed an elevated mean pulmonary artery pressure (mPAP) with normal wedge pressures (Table 2). The results of the RHC and the entire workup for pulmonary arterial hypertension (PAH) confirmed the diagnosis of idiopathic pulmonary arterial hypertension or IPAH (which at the time was referred to as primary PH). Due to a pending geographical move, no therapy was initiated until she established care with our PH center 4 months later.

Monitoring and Management: When the patient established care at our center, she was initiated on intravenous (IV) epoprostenol. At the time, epoprostenol was the only Food and Drug Administration (FDA)-approved medical treatment available. She experienced significant improvement clinically (World Health Organization [WHO] symptoms improving from class III to II), functionally (improved 6-minute walk test [6MWT] from 240 m to 400 m), and hemodynamically (cardiac ECHO showed improved RV function to mild...
hypokinesis and decreased PASP to 50 mm Hg).

Three years later, she developed worsening DOE despite increasing IV epoprostenol dosage. She declined recommendations to be evaluated for lung transplantation, instead opting to continue with only medical therapy. In 2002, when bosentan (which was an oral endothelial receptor antagonist) approved by the FDA, it was also added to her medical regimen and she experienced significant improvement in her symptoms. Several attempts to titrate down her IV epoprostenol were unsuccessful. She continued to be clinically stable for several years until 2007, when she again developed clinical worsening. Her 6MWT distance decreased to 230 m, and she now desaturated to 85%. Her b-type natriuretic peptide (BNP) level was elevated at 500 ng/L, and a repeat RHC revealed worsening of her hemodynamic parameters (Table 3). She was again offered evaluation for lung transplantation but again declined. Sildenafil 20 mg 3 times a day was started along with 2 L oxygen. This additional therapy improved her symptoms and she remained stable on triple therapy.

In 2010, on maximal therapy, her symptoms dramatically worsened (WHO class IV, 6MWT: 200 m, desaturation to 86% on 2 L nasal cannula), with a rise in BNP level to 800 ng/L. An ECHO showed her PASP to be 90 mm Hg, with worsening of her RV dilation and now with severe RV hypokinesis (Figure 3). She was finally evaluated and listed for lung transplantation. Her lung allocation score (LAS) upon listing was 34, which clearly did not reflect how severe her disease was. Because of her severely elevated right atrial pressure (RAP), decreased cardiac index (CI) (RAP >15 mm Hg and CI <1.8 L/min/m²), and continued clinical decline despite optimal medical therapy, she was granted exception points on the LAS and her score was increased to the 90th percentile.

At the age of 42, our patient underwent bilateral lung transplantation (BLT) 2 months after being placed on the list. This was 11 years after first being diagnosed with IPAH and after being on a 3-drug regimen for 3 of those 11 years. She had no significant postoperative complications. Her cardiac ECHO 1 month postoperatively showed resolution of her prior RA/RV dilation and hypokinesis, with dramatic improvement in PASP from 90 mm Hg preoperatively to 31 mm Hg postoperatively (Figure 4). She is now back at the gym 5 times per week, has a personal trainer, and runs 2 miles every day with
only minimal dyspnea—a stark contrast to before her lung transplant.

DISCUSSION: Despite being on maximal combination medical therapy including a prostacyclin, our PAH patient had progressive clinical and hemodynamic worsening. For her and many other patients with PAH who fail available medical therapy, lung transplantation is the best therapeutic option. This patient’s long journey with IPAH up to and including lung transplantation demonstrates many key concepts inherent to the management of PAH, including how the assessment and management of PAH has changed over the last 15 years. Before the development of the first approved medical therapy in 1995 (epoprostenol), lung transplantation was the only option available for patients with PAH. At that time, 11% of all lung transplants were performed for patients with PAH.1 Since that time, 12 medications have been approved in the United States for PAH. The use of these medications has made it possible to delay and in some cases decrease the number of patients actually requiring a lung transplant. This benefit is reflected in the fact that in 2015, and over the last few years, fewer then 3% of all lung transplants performed were for patients with PAH (Figure 5).2

Unfortunately, patients with PAH are often referred for lung transplantation when their disease has significantly progressed. At the time of referral, they may already have poor prognostic markers, which may limit their survival and ability to survive long enough on the waiting list to receive an organ. PAH patients can have waitlist mortalities as high as 30%.4 Thus, education and early referral is key. Historically, referral of PAH patients has been delayed by a lack of awareness on the part of physicians and patients alike regarding how rapidly this condition can progress to hemodynamic instability and irreversible right heart failure. Often, this results in physicians missing a pivotal time window when interventions can actually affect outcomes.

The 2014 International Society of Heart and Lung Transplantation (ISHLT) guidelines recommend referral of the following PAH patients for lung transplant evaluation: a) WHO III or IV symptoms with escalating therapy, b) rapidly progressive signs/symptoms, or c) patients started on parenteral therapy.2 The 2015 European Respiratory Society (ERS) guidelines include similar recommendations, but simply advocate for referral soon after noting an inadequate response to maximal combination therapy.5 A recent state-of-the-art review by McLaughlin recommends referral before severe RV dysfunction develops to ensure positive outcomes in such a high-risk group.6

The 2014 ISHLT guidelines2,7 recommend listing a patient for transplant when patients have persistent WHO class III or IV symptoms despite combination medical therapy for at least 3 months, have severe functional limitation on a 6MWT (<350 m), or possess severe hemodynamic abnormalities on RHC, including a CI <1.8 L/min/m² and a mean RAP of >15 mm Hg, as well as markers of poor prognosis such as worsening right heart function, hemoptysis, and pericardial effusions.5,8 This patient met these criteria, but despite counseling, she continued to refuse lung transplantation for several years.

In general, patients with PAH receive lower LAS ratings when compared to other diagnostic groups. This translates into longer wait times on the list and increased mortality rates. The United Network of Organ Sharing (UNOS) offers “exception points” to patients with PAH if they meet certain criteria. The transplant center must apply to a UNOS committee for full review to obtain these points for their patients. These exception points can be added to the LAS if the following criteria are met: 1) deterioration on optimal medical therapy, 2) RAP >15 mm Hg or CI <1.8 L/min/m². Our patient’s LAS was only 34, but she was granted exception points that were key in allowing her to obtain a lung transplant as early as she did.

Historically, combined heart and bilateral lung transplantation was initially

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Table 3. RHC data while on IV epoprostenol and bosentan

Figure 3: Transthoracic ECHO (4-chamber view) while on triple therapy (IV epoprostenol, PO bosentan, and PO sildenafil) showing continued worsening of her dilated right-sided chambers, now with septal bowing toward the left ventricle.

Figure 3: Transthoracic ECHO (4-chamber view) while on triple therapy (IV epoprostenol, PO bosentan, and PO sildenafil) showing continued worsening of her dilated right-sided chambers, now with septal bowing toward the left ventricle.

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The 2014 ISHLT guidelines2,7 recommend listing a patient for transplant when patients have persistent WHO class III or IV symptoms despite combination medical therapy for at least 3 months, have severe functional limitation on a 6MWT (<350 m), or possess severe hemodynamic abnormalities on RHC, including a CI <2 L/min/m² and a mean RAP of >15 mm Hg, as well as markers of poor prognosis such as worsening right heart function, hemoptysis, and pericardial effusions.5,8 This patient met these criteria, but despite counseling, she continued to refuse lung transplantation for several years.

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Historically, combined heart and bilateral lung transplantation was initially

Table 3. RHC data while on IV epoprostenol and bosentan
the preferred transplant procedure for patients with PAH. However, after it was discovered that the RV could recover after just a lung transplant alone, isolated BLT became the procedure of choice. There is a subset of patients who still require combined heart and bilateral lung transplantation, either because they have intractable right heart failure secondary to permanent cardiac remodeling, dependence on inotropic support, or coexisting left heart disease. Previous studies looking at single lung transplant (SLT) vs BLT revealed that BLT showed superior outcomes, largely because of improved perioperative hemodynamics (Figure 6). Consistent with this, our patient and more than 90% of patients with PAH over the last 15 years have received BLTs. In a recent study, however, Julliard highlighted a single center’s experience showing comparable outcomes between SLTs and BLTs regardless of the severity of the underlying PAH. These results will need to be assessed further in a larger study.

Our patient had worsened clinically prior to transplantation, but did not develop significant hemodynamic instability. Others, however, may not be as fortunate. These patients often may need aggressive therapy for right heart failure as a “bridge to transplantation.” Some of the therapies that may be used are atrial septostomy or extracorporeal membrane oxygenation (ECMO), the latter of which is used more commonly in the United States. When used as a bridge to transplant, ECMO is a life-prolonging therapy until donor organs become available. ECMO can prevent the development of further end-organ damage by maintaining perfusion to the rest of body. Potential complications of ECMO include vascular access injury, infection at the cannulation sites, hemorrhage, renal failure, neurological complications, and thromboembolic risk. It should only be utilized in well-selected patients and within experienced centers.

Compared to other diagnostic groups, patients with PAH have a higher mortality rate early after lung transplantation due to the increased requirement for cardiopulmonary bypass, preoperative RV dysfunction, and increased risk of ischemic-reperfusion injury during the perioperative period. In fact, 3-month survival for PAH patients is 78%, compared to 86% for idiopathic pulmonary fibrosis (IPF) and 91% for cystic fibrosis and chronic obstructive pulmonary disease (COPD). These outcomes highlight the importance of providing PAH patients with aggressive hemodynamic support and close surveillance in the early postoperative period. However, if patients survive the first year, they will have similar outcomes to the other diagnostic groups up to 5 years post-transplant. In the long term, PAH patients actually have among the highest 10-year survival rates at 45%, compared to 28% for COPD and IPF (Figure 7). This patient is now more than 5 years post-transplant and is currently running marathons and traveling the world with her family. She is showing every indication that her outcomes will be just as promising if not more.

**Teaching Points**

1. PAH patient with escalating therapy should be followed closely with fre-
quent follow-up visits because of the rapidly progressive nature of this disease, requiring frequent therapeutic adjustments.

2. The following patients with PAH should be placed on the transplant list:
   a. WHO functional class III or IV symptoms despite a trial of at least 3 months of combination therapy including prostanoids
   b. CI of <2 L/min/m²
   c. Mean RAP >15 mm Hg
   d. 6MWT <350 m
   e. Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, BNP, or recurrent ascites)

3. After listing, lung transplant centers may apply for exception points to the LAS if the following criteria are met:
   a. Deterioration on optimal medical therapy
   b. RAP >15 mm Hg or CI <1.8 L/min/m²

4. Bilateral lung transplantation is currently the preferred and most commonly used operation for patients with PAH. However, for a subset of patients with intractable right or left heart failure dependent on inotropic support, combined heart-lung transplantation is still performed.

5. If life-threatening RV failure develops before lung transplant, bridging with aggressive therapies such as ECMO can be used to prevent the occurrence of secondary organ injury.

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Dealing With End-Stage Pulmonary Arterial Hypertension

Dr. Farber: Let's start by introducing today's group for this discussion. I'll start with Olivier.

Dr. Olivier Sitbon: Hello, I am Olivier Sitbon. I am Professor of Respiratory Medicine at the South Paris University, France; Maria Crespo, associate medical director of the lung transplant program at the University of Pittsburgh; and Adaani Frost, professor at the Institute of Academic Medicine, and director of the Houston Methodist Lung Center.

Dr. Farber: Maria, how do you see this? How would you view this as a transplant physician?

Dr. Crespo: Yes, I think I agree with Adaani. I think end-stage pulmonary hypertension should be considered in those patients who have failed all types of medical therapy and lung or heart-lung transplantation, is the only option for them. Mechanical circulatory support as a bridge for lung transplantation should be considered for those patients who have developed end-stage pulmonary hypertension and and refractory right ventricular failure.

Dr. Farber: For us, all being in Western Europe or the United States; I assume we would consider somebody who has not yet received systemic prostanoids not a failure or end-stage.

Dr. Frost: That's sort of defined by 2 things. Number 1, that you're at the end of your therapeutic alternatives from a medical point of view; and number 2, that the hemodynamic and echocardiographic features of the right ventricle indicate that that muscle on which life is dependent is starting to fail. So, it's a combination of where you are in the therapeutic algorithm and how the right ventricle and the pulmonary vascular bed is responding to that.

Dr. Sitbon: For me, lung transplantation is included into the treatment strategy.

Dr. Farber: Okay, Olivier, do you like that definition or would you change it at all?

Dr. Sitbon: No, I agree with Adaani. When she says about the no therapeutic alternatives, do you include lung transplantation withing the alternatives?

Dr. Farber: Maria, how do you see the no therapeutic alternatives, since you're replacing the organ your ability to modify the organ and let the patient live out their life with the lungs that God gave 'em is gone. So I consider lung transplantation, while it's a major therapy, it is from my perspective, as a pulmonary hypertension doctor, it's kind of an admission of failure. It means that you've reached the point where you can't modify the disease, and now you have to replace the organ.

Dr. Frost: I meant “no medical” therapeutic alternatives, since you're replacing the organ your ability to modify the organ and let the patient live out their life with the lungs that God gave 'em is gone. So I consider lung transplantation, while it's a major therapy, it is from my perspective, as a pulmonary hypertension doctor, it's kind of an admission of failure. It means that you've reached the point where you can’t modify the disease, and now you have to replace the organ.

Dr. Farber: So, Olivier, you would consider a patient as end-stage as somebody who, for whatever reason, does not qualify for, or cannot obtain lung transplantation.

Dr. Sitbon: Yes, that's correct.

Dr. Farber: This is very interesting. As an aside and of interest to this discussion, I just returned from New...
think about it earlier, perhaps do it sooner. The hard thing is trying to find where the line in the sand is. Is that a paraphrase?

Dr. Farber: Why do the French look at this differently than we Americans do?

Dr. Frost: Maybe because they can get them transplanted earlier. We really have a terrible time... if you know that the patient has failed therapy after therapy and if the RV is looking bigger and the cardiac index is getting smaller, we still cannot get them transplanted, so listing them is moot if the Lung Allocation Score does not permit them to be transplanted. By the time it permits them to be transplanted, quite frankly, a bunch of these people are really almost too sick to be transplanted. We're doing salvage therapy on patients who increasingly, embarrassingly, are at the edge where salvage becomes harder and the complications of transplant become more. I think the French, and possibly the Germans, too, Olivier you can tell me, are much faster about moving them down the transplant line, and they don't have the same restrictions, I suspect, to getting them transplanted.

Dr. Sitbon: Yes, yes. I can give you some information about the system of lung allocations in France, in particular, for patients with refractory right heart failure in the setting of pulmonary hypertension. We have the possibility for those patients who are hospitalized in intensive care unit on the maximal medical therapy, including IV prostacyclin. For PAH on triple-combination therapy, including IV prostacyclin, refractory to this association, we have the possibility to put them on the very urgent transplant list, and those patients are awaiting for a graft for a maximum of 15 days. Usually those patients are transplanted within the time frame, so 15 days is the maximum listing for highly urgent list, and usually we are able to transplant them during this time.

Dr. Crespo: Olivier, were any of those patients on ECMO?

Dr. Sitbon: Sometimes. Sometimes we bridge them on ECMO. We did that for maybe 4 or 5 patients, but usually it is possible to transplant them without needing a bridge with ECMO, so we have a very good result with this kind of strategy, and we transplant a lot of patients. Last year, we transplanted 50, five-zero, patients with PH in our center, fifty.

Dr. Crespo: So, patients who are waiting for a lung transplant in France, if they are on ECMO, do they have a higher chance of getting a lung transplant soon?

Dr. Sitbon: No, at this time, it's the same. Patients on ECMO are highly, highly, highly urgent, of course, but for patients in ICU needing inotropic support, the main criteria are inotropic support, dobutamine, and/or epinephrine. For those patients on the maximal medical therapy for PAH plus inotropic support, we can list them on the transplant program, and usually they are transplanted within 15 days. Sometimes it's hours.

Dr. Crespo: Going back to what Adani was mentioning before that the definition of severity/urgency of listed patients with pulmonary hypertension for lung transplant that you use is basically the same criteria as the ISHLT, depending on the functional status and some of the hemodynamic findings in these patients, so who are really the patients that you will consider to be evaluated sooner for a lung transplant?

Dr. Sitbon: I said previously that these patients with PAH on the maximal combination therapy and that have the right heart failure, needing inotropic support. Another indication is of a patient with pulmonary veno-occlusive disease, because we have a lot patients with PVOD and those patients are usually listed very quickly after the diagnosis of the disease. We start monotherapy and we list them very quickly, but to be on the urgent transplant list, they have to be in intensive care unit with inotropic support. Those are the only criteria.
Dr. Frost: You know, I have had patients in the ICU for a month-and-a-half and not been able to get them transplanted.

Dr. Farber: Yes, we have had the same problems.

Dr. Frost: Partly, what we're doing is we'll admit inpatients into the ICU. We know they’re at the end of their medically managed therapeutic options; they are requiring frequent hospitalizations as we start an inotrope to increase their LAS score and help to get them transplanted. At this point, they're having multiple admissions, their kidney function is starting to deteriorate, but the minute they start showing features that identify them as high risk, it can actually count against them. So worsening parameters of disease are associated with worse post-transplant outcomes. Then their Lung Allocation Score is skewed against transplant, so we are really in a very bad position. The European treat-to-goal paper demonstrated very nicely that moving people down the algorithmic tree of therapy very briskly based on achieving milestones, such as inadequate walk, the resolution of functional class 3 to a functional class 2, and MVO2, etc., and adding therapy including transplant to achieve those goals resulted in better survival. It would not be possible in the US to get a patient transplanted who is a persistent functional class 3 and a walk that was less than 300. So we end up then with people with deteriorating renal function, passive congestion of the liver, liver compromise without a transplant option—and it's a huge issue.

Dr. Farber: Maria, I would assume that the French and UPMC are using very similar criteria for transplant eligibility.

Dr. Frost: Doesn't sound like it.

Dr. Farber: It doesn’t sound like it, exactly. And I agree, it does seem that it takes longer in the US to get PAH patients considered for and/or transplanted than it does in Paris. Is that true? If so, how do we fix it? Does it make a difference? Seemingly, it does.

Dr. Crespo: The February 2015 revised LAS scoring system includes measurements of heart function and heart failure that will result in a more accurate predicted risk of wait-list mortality in patients who have pulmonary hypertension so patients who have PH are expected to have higher LAS, increasing to 90% percentile in some patients with PH and right ventricular failure. I think it's very early to assess the impact of the new revised LAS changes on survival in patients with PH before considering adding other values like ECMO and other markers of poor outcome.

Dr. Frost: I mean the concept that in our patients who are on as much therapy as we can reasonably give them, do not really enter into the transplant arena until they have a right atrial pressure of 15 or greater or a cardiac index of less than 1.8. At that point in time, when you have no other therapies except transplant, the concept that this is the point in time that you are listing them is the antithesis of the approach, for instance, of renal transplant, where the earlier you can do the transplant the better—and we are being preemptively listed before they're even dialyzed now. And that is where they show the greatest, most valued both quality of life improvement, health care dollars improvement, and the highest survival rate, but we're doing the exact opposite of that in lung transplantation in the United States. We are skewing the curve to the point where either people can't get transplanted, or the ones who are getting transplanted are such breathtakingly high risk that the incidence of primary graft dysfunction, early rejection, bronchiolitis obliterans, death within one year, are all stacked against the PAH patient. There’s something very wrong with this system.

Dr. Farber: If that's true, how do we change it?

Dr. Frost: Well, the lung transplant—the United Network of Organ Sharing and the fact that lung transplant is a Medicare-approved, Medicare-funded process means that they're only gonna respond to data, and I think there's been a lot of data generated from UNOS/OPTN that was incorporated to even get them to produce the modifications in the Lung Allocation Score to provide us with the meager exceptions we have, but I think that maybe it's time to go back to the drawing board. You know, Olivier, Marius Hoeper, and a lot of European researchers particularly have done a lot of work looking at predictive markers of RV dysfunction which are indicative of the point in time at which the RV kind of reaches the point of no return, and what predicts the rapid evolution of that point of no return, the point at which the RV is so dysfunctional that the patient's risk of mortality and secondary organ dysfunction, like liver, kidney, etc., starts to occur with a greater likelihood. That is what we need to have and we need to be able to take that to UNOS and say these are more reasonable early predictors of mortality. We are currently skewing the likelihood of death with the transplant by transplantaing people who are much too sick. So data are what we need, and that means things like biomarkers, echocardiographic markers, in a more scientific way than we’ve been generating today.

Dr. Crespo: I agree, yes.

Dr. Farber: I would agree, especially given the seeming disparity between the two sides of the Atlantic. How do we generate these data; they should be available?

Dr. Frost: If you look at the data on lung transplants for PAH patients, if they survive beyond a year, they do great, but the greatest risk is within the first six months post-transplant and the survival statistics at their centers might not actually help provide us with the data that we need to be able to assess if and where US PH transplant indices can be improved. My sense is that in the US we either disenfranchising PAH patients or we're transplanting people too late in the course of their therapy, and I think that the European data might inform us. Olivier, you publish your own transplant data, or do you put it in ISHLT where it's either sporadically entered or diluted out by other centers without your level of expertise?
Dr. Sitbon: I think all our cases are included in the statistics of the interventional statistics for following transplant, and the results we have in patients with PAH are about similar to that was observed in other centers, so the survival after lung transplant is worse than for the other indication, than lung transplant for the other indications. It is shorter during the 6 months; first 12 months, the mortality did increase in those patients. However, if we are not doing lung transplants in those patients, the spontaneous survival is very, very poor. So that’s why we decided to put pulmonary arterial hypertension at the top of the list for lung transplantation besides refractory lung fibrosis. For example, in our center, we never transplant patients with emphysema, never. We consider that the spontaneous outcome of those patients is similar to the outcome with a transplant. So we really think that lung transplant is a very important option for patients with pulmonary arterial hypertension and also for patients with—and in particular patients with—pulmonary veno-occlusive disease. But we know that the results are worse after, but if we are waiting for at least 1 year, the results after 1 year are similar to the other, so we have the same result as in other centers.

Dr. Farber: Okay, since we brought up the topic, let's talk about mechanical support for the right ventricle: ECMO, RVAD, or any other device. Where do we think we are with these devices? Do we use them at all, do we use them strictly as a bridge to transplant, or do we consider their use as a bridge to treatment? In sum, how do we currently view any of these devices and their use?

Dr. Sitbon: Okay. Today we consider this kind of support, ECMO, or mini ECMO, only for bridging patients to lung transplant. I know that to use this kind of system, ECMO for example, to recovery or waiting for the efficacy of drugs could be an interesting approach, but I think that today no one or almost nobody has the experience of that. I discussed with Marius Hoepers a few months ago about that. I think he used this kind of technique only in 1 patient as a bridge to recovery not bridge to lung transplantation. But now with the use of first-line combination therapy, they are very, very quickly efficacious and I think with this kind of approach of first-line combination, I am not sure that we need really mechanical support awaiting the efficacy of drugs. For the other patients, patients already treated with two or three drugs, including prostanlycin, I think if we consider mechanical support, this can be done only in patients awaiting lung transplants. That’s my point of view.

Dr. Crespel: Yes, I agree. We use ECMO on patients who have developed end-stage diseases, as a bridge for lung transplantation. We use ECMO support in selected patients with profound respiratory failure secondary to lung disease and refractory as a bridge for lung transplant.

Dr. Frost: There’s what we do, and then there’s what is discussed in the literature, and we’ve used VV-ECMO for people who have decent sized right-to-left shunts where their RV is failing and they are hypoxic because it's much less invasive than veno-arterial. We've done veno-arterial ECMO more frequently, but it is still rare; and if we can't get them very quickly to transplant, our results are not good. Dr Shaf Keshiavee has published an aggressive management protocol in Toronto with patients who were failing with pulmonary hypertension. They’ve reached the end of—as I understand it, they've reached the end of their therapeutic algorithm, they’re still in marginal heart failure, there’s nothing else that can be given for them, they’re listed for transplantation, and this is ECMO as a bridge to transplant or just a Novalung. Most of the data, as Olivier alluded to, I think, about a bridge to recovery, and in this instance the North American data, is not very good. I think Erika Rosenzweig published a paper looking at outcomes of PH patients with potentially reversible disease where ECMO was used as a bridge, but the results were dismal. I don’t think there were any long-term survivors. There were a few short-term survivors—people who survived to removal of ECMO, but did not survive the hospitalization. The same was not true, as Olivier alluded to, for the bridge to transplant, where it was a very successful intervention that allowed a patient to survive to transplant. The role of RVADs in the future, however, is unclear to me. We’re clearly very bad at figuring out when the RV is failing, so to do a bridging maneuver with a VAD, which has its own complications (hemolysis, the operation itself) and importantly you have not dealt with the afterload of the right ventricle, you’re just putting in a stronger pump. This is fraught with questions. When RVADs have been laced they have not been terribly successful. I think putting in a VAD when you haven’t done anything about the afterload is probably as useless in RV failure as it is in LV failure. I mean, you have to have somebody optimally treated if their left ventricle is failing and the LV is still bad before you put in a VAD or a total heart for that indication. You don’t put it in somebody with uncontrolled systemic hypertension. So I guess the point is that we’re skewing the results for any utility for right ventricular assist devices for pulmonary hypertension because of our own inability to appropriately reduce the resistance in the pulmonary vascular bed, so I have no idea what will be the role of our outcome of RVADs in the future, in future management of PH.

Dr. Farber: So, Olivier, in regard to Adaani’s last question, is there any future for RVADs in PH, and if so how would we do this?

Dr. Frost: You get the easy questions (laughter).

Dr. Sitbon: Easy questions. The future for RVADs, that is the question? I think today we cannot consider RVADs outside of bridging to lung transplantation. Maybe if we can miniaturize...
Dr. Farber: Maria, what do you think?

Dr. Crespo: There’s not much data on the efficacy of RVADs on this condition. We haven’t used right ventricular assist devices in refractory and/or end-stage PAH with RV failure.

Dr. Farber: I think the main point is one that Adaani has made: just sticking an assist device into a ventricle without somehow changing the resistance of the pulmonary circulation is unlikely to be successful. And if we define somebody as refractory PAH because we can’t control their resistance, I don’t really understand, at least currently, how an assist device is going to be beneficial. Moving on to a few other topics: Olivier, do you use or perform atrial septostomies?

Dr. Sitbon: No, no. Usually we don’t use atrial septostomy. We sometimes indicate the Potts surgery for children and we have very good results in children with suprasystemic pulmonary hypertension.

Dr. Farber: Right, you have published on that.

Dr. Sitbon: And we have very, very nice results with the Potts surgery and recently we had two cases of not children, but teenagers, who had not the Potts surgery but Potts intervention via endovascular—

Dr. Farber: We’ve done some of those, too.

Dr. Sitbon: And it was successful in 2 teenagers. I think it is a quite difficult intervention, endovascular intervention, but it seems that the results are very, very good. In all patients we did Potts surgery, we were able to wean off epoprostenol.

Dr. Farber: Adaani?

Dr. Frost: We’ve done some septostomy. Because we’re affiliated with Texas Childrens, there were a fair number in the pediatric patient population up into early adulthood. In addition, under my watch here in adults, we did 2 or 3. The first one failed acutely due to hypoxia. The concept of multiple sequential mild dilations had not been reported. Another anorexia-associated PAH simply wasn’t sufficient to benefit the patient. In contrast, the data from Julio Sandoval is spectacular, reflecting the level of his expertise, and that is not something we’ve been able to reproduce.

Dr. Farber: The other subject I would like to discuss is palliative care for these end-stage patients. When should we do it? How do we do it? Do we do it enough? Are we afraid to do it because to some of us it seems as if we are giving up? How do we go about making it better? I’ll start with the Americans and then let Olivier have the last word. For example, these are patients that have end-stage disease, have received all possible medical therapies, either don’t qualify for transplant for whatever reason, and seemingly there is no alternative remaining. Somehow, many of us always think that there may be another treatment because we find it difficult to admit that we cannot do anything else (in a way that we are defeated). How do we deal with this?

Dr. Crespo: All patients who come for lung transplant evaluation are being evaluated by palliative care. This has been very beneficial helping patients cope with their disease and prognosis. This approach has also helped prepare patients and their families with end-of-life decisions.

Dr. Frost: You know, maybe you’re better at it than we are, Maria, because you have this built in sort of palliative care initiative with your transplant program, but to PAH patients it’s a difficult subject to broach. Interestingly, I never have much push-back from transplant patients if they were told they weren’t transplantable, but there is a fair bit of resistance with the PAH patients. I think it’s maybe because they were at time of diagnosis told that they had a horrible disease with a high mortality, and yet many of them have lived two, three, four times their projected lifespan, and they’ve done that because the drug evolution has been such in the last 15 years that just as they reach the end of one drug’s maximum effect, another one has come along to sort of bail them out, and I think that the number of studies, the number of new drugs, the fact that so many of them have survived already against the odds that are huge actually has proven to be an interesting but difficult issue. It makes them very willing to go into a study, but I think it makes them a little unwilling to accept their own mortality. The ones who do are quite often older and are simply tired of being sick. For younger patients, it can be brutal for them, particularly if they have survived to see their children grow into early adulthood and they have expectations now that the science will continue to stay one leap ahead of their disease. So to answer your question, I think that we’re bad at palliative care, I think there are some things that are unique to our patient population. I do two things when I start a patient on an IV drug. I refer them for transplant because I know it’s my last and best drug, and I will quite often start talking to them about palliative care, what are we going to do if, if they’re turned down for transplant and if this drug doesn’t work, and it does not seem to have made my issues or the patient’s issues any easier or any smoother.

Dr. Sitbon: I think that patients with end-stage disease or refractory right heart failure without an indication for transplant or because it’s not possible have the same picture that we are doing for patients with cancer—the question for those patients is what is the, how do you say that, the level of treatment we have to apply, we have to push the treatment up to what kind of level? What are our expectations? If it is really end-stage disease, if we don’t have any option for them, I think that the question of down-titration of drugs have to be addressed because we know that we have patients with a lot of side effects with very high-dose epoprostenol, for example, and they are refractory to these kinds of treatment and we have no other option, so what are the maximum levels to reach in those patients. It’s exactly like for cancer. In a patient with cancer, we try chemotherapy, then a second one, then a third, and what is the next option. Well usually we don’t know, and we consider palliative care in those patients, and I think it’s exactly the same for patients with PAH. They both are very similar diseases.
Dr. Farber: Okay. This was a terrific session. Does anybody have any last words they’d like to add or anything that we missed?

Dr. Frost: I’m sure we missed something (laughter).

Dr. Farber: Only lunch—(laughter).

Dr. Farber: Adaani, Maria, Olivier, thanks a lot. I appreciate your time and effort. This was such a worthwhile discussion of a very difficult topic.

NEWS TO USE

Help improve your PH patients’ access to their prescribed treatments.
The Specialty Pharmacy Feedback Form—an initiative of PHA and the Caring Voice Coalition—provides an opportunity for you and your patients to let SPs know what they’re doing well and where they can improve. Input from medical professionals helps the Specialty Pharmacy Advisory Board identify trends and best practices in the specialty pharmacy field. Submit your comments at: www.PHAssociation.org/SpecialtyPharmacyForm.

Help ensure PH care for all!
Support your colleagues as they seek to identify additional barriers encountered by underrepresented minorities and socioeconomically disadvantaged patients seeking PH diagnosis and treatment. Please take our brief survey, as the committee seeks to identify the populations most affected by these barriers, as well as the barriers themselves. https://www.surveymonkey.com/r/PHCareforAll

About PH Care for All:
Progress in treatment of pulmonary hypertension (PH) and the organization of the PH community has been substantial over the past 25 years. The PH field has progressed from zero treatments to 14, which is as many or more than all but 2 of the roughly 7,000 rare diseases. Medical research and knowledge in the field is expanding rapidly.

Early data collected through PHA’s Envelope of Hope program is beginning to show that PHA’s Early Diagnosis Campaign is making headway in terms of the average time from onset of symptoms to point of diagnosis; however, research findings presented at the 2014 meeting of the American Thoracic Society by Cardenas-Garcia et al indicate that underrepresented minorities and socioeconomically disadvantaged patients are impacted disproportionately by the most common barriers to PH diagnosis, as well as by a number of additional barriers unique to these populations. These barriers not only adversely affect the PH diagnosis itself, but also impact patients’ ability to receive treatment once the diagnosis has been made. With preliminary data indicating that these patients experience diagnostic delays beyond the mean of 2.8 years indicated by REVEAL, the concern is that many of these patients are missing the window for treatment and intervention entirely. As PHA continues to positively impact the average time to PH diagnosis, we must ensure that the additional needs of ethnic minorities and socioeconomically disadvantaged patients are met.

From this desire, PH Care for All was born. The committee, consisting of 23 expert clinicians and academicians committed to reaching these vulnerable patients, is led by Vinicio de Jesus Perez, MD, and Arunabh Talwar, MD. With this initiative, the PHA continues its commitment to advocating for PH patients by educating health care providers and building a foundation for new health policies that will favor this vulnerable patient population. Our ultimate goal is to ensure that all PH patients receive the same level of care regardless of ethnicity, socioeconomic status, or race. In short, we’d like to ensure PH care for all!

Start a support group at your practice!
Hundreds of PH-treating physicians and allied health care professionals play a vital role in the success of PH support groups. Support group participation helps with patient compliance, as patients learn about the disease, gain coping skills, and find the emotional strength to keep fighting.

According to our latest census, which surveyed 160 leaders, half of our support groups meet in hospitals or clinics. Nearly 60% of meetings have speakers, 82% of which have a medical background. As a medical professional, you have the resources groups are looking for: a meeting space and expertise. Let PHA do the rest, providing food sponsorship and publicity. Start a support group at your hospital or clinic by contacting MichaelK@PHAssociation.org today.
What is the role of nitric oxide (NO) in PAH and CTEPH?

- PAH and CTEPH are associated with impaired synthesis of NO, endothelial dysfunction, and insufficient stimulation of the NO-sGC-cGMP pathway.
- Intracellular cyclic guanosine monophosphate (cGMP) plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation.

Adempas stimulates sGC regardless of NO level to produce more cGMP

- Adempas sensitizes soluble guanylate cyclase (sGC) to endogenous NO by stabilizing sGC-NO binding.
- Adempas directly stimulates sGC independently of NO via a different binding site.
- Increased cGMP leads to vasodilation.

INDICATIONS

- Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.
- Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.*

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

*Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY
Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.

CONTRAINDICATIONS

- Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.
Take your PAH and CTEPH patients farther with Adempas

In pulmonary arterial hypertension (PAH), (WHO Group 1)

36m improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 443 adult PAH patients with predominantly WHO Functional Class II-III. The primary endpoint was change from baseline in 6MWD at 12 weeks.

CONTRAINDICATIONS (continued)

- Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity. Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program.

Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

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ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION
For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning

• Do not administer Adempas to a pregnant female because it may cause fetal harm (4.1, 5.1, 8.1)
• Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, 8.6)
• For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).

1 INDICATIONS AND USAGE
1.1 Chronic-Thromboembolic Pulmonary Hypertension
Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].

1.2 Pulmonary Arterial Hypertension
Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].

2 CONTRAINdications
2.1 Pregnancy
Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

2.2 Nitrates and Nitric Oxide Donors
Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

2.3 Phosphodiesterase Inhibitors
Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

3 WARNINGS AND PRECAUTIONS
3.1 Embryo-Fetal Toxicity
Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program [see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)].

3.2 Adempas REMS Program
Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program [see Warnings and Precautions (5.1)].

Important requirements of the Adempas REMS Program include the following:
• Prescribers must be certified with the program by enrolling and completing training.
• All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
• Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)].
• Pharmacies must be certified with the program and must only dispense to pharmacies that are certified with the program. A list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

3.3 Hypotension
Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors [see Drug Interactions (7.2) and Clinical Pharmacology (12.2)].

Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding
In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease
Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed elsewhere in the labeling:
• Embryo-Fetal Toxicity [see Warnings and Precautions (5.1)]
• Hypotension [see Warnings and Precautions (5.4)]
• Bleeding [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years [see Clinical Studies (14.1, 14.2)].

The safety profile of Adempas in patients with inoperable or recurrent/ persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16 week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsia and Gastritis</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

DRUG INTERACTIONS
7.1 Pharmacodynamic Interactions with Adempas
Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)].

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension [see Contraindications (4.2) and Clinical Pharmacology (12.2)]. Clinical experience with co-administration of Adempas and
other phosphodiesterase inhibitors (for example, milrinone, cilostazole, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who may not tolerate the hypertensive effect of riociguat [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungals (for example, itraconazole, ketoconazole), or H1 or H2 protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see Clinical Pharmacology (12.3)].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity with exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see Boxed Warning and Contraindications (4.1)].

Animal Data

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significant compared to controls for the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and human. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/ day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5, and 5 mg/kg/day, an increase in spontaneous abortions was observed starting at the middle dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk, and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall differences in safety or effectiveness were observed in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients showed a higher exposure to Adempas [see Clinical Pharmacology (12.3)].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [See Boxed Warning].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 ml/min or on dialysis [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzable.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide), Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. Instruct females of reproductive potential to use effective contraception and to contact their physician if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see Warnings and Precautions (5.2)]. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

• All female patients must sign an enrollment form.
• Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [See Use in Specific Populations (8.1)].
• Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
• Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

• Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
• Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
• Instruct patients on the dosing, titration, and maintenance of Adempas.
• Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
• Advise patients that antacids should not be taken within 1 hour of taking Adempas.
• Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see Adverse Reactions (6.1)]. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

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Program Announcement:

New Application Deadline: October 12, 2016
New Application Deadline: February 12, 2017

Resubmission Deadline: July 12, 2016
Resubmission Deadline: November 12, 2016

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Mentored Clinical Scientist Development Award (K08) &
Mentored Patient-Oriented Research Career Development Award (K23)

PURPOSE: K08

- To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
- To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
- To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
- To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

PURPOSE: K23

- To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
- To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
- To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
- To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

MECHANISM:

Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 or the K23 mechanism.

FUNDING:

The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2016.

Learn about all of PHA’s research opportunities at www.PHAssociation.org/ResearchProgram

* Restrictions apply. Please see complete announcement at the website listed above.