Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population

LUNCHEON SYMPOSIUM

Monday, August 1, 2016
1:00 p.m. – 3:20 p.m.
Los Angeles Convention Center
Room 408A
Los Angeles, California

Supported by educational grants from Actelion Pharmaceuticals US, Inc.; Gilead Sciences, Inc.; and United Therapeutics
FAMILY MEDICINE SECTION

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SYLLABUS

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Faculty Disclosures of Commercial Relationships

WARREN A. JONES, M.D.¹

LESLIE KINGSLOW, M.D.
Advisory Board: United Therapeutics, Gilead
Speakers' Bureau: Gilead

ALEM MEHARI, M.D.¹

OCTAVIUS POLK, M.D.¹

¹This speaker declares no relevant relationship with commercial entities.
Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population

Introduction
Pulmonary arterial hypertension (PAH) encompasses associated forms of the disease, induced by secondary disease states which cause stress and injury to the pulmonary vascular bed potentiating progressive pulmonary vasculopathy (including scleroderma/mixed connective tissue disease/SLE; HIV; portal-hepatic disease; sickle cell disease; and offending drugs and toxins). Many of the associated forms of PAH (APAH) disproportionately affect the African American population, particularly scleroderma and other connective tissue diseases, medicine, HIV, vaccine, cirrhotic liver disease/viral hepatitis/portal hypertension and Sickie Cell Disease.

Although this disease process has become more well recognized, many primary care providers, physician extenders, and medical subspecialists still often do not consider this disease in their differential diagnoses due to an overwhelming lack of understanding of pulmonary arterial hypertension in the medical community. Hence, this disease remains misdiagnosed, sorely under-recognized, under-treated and mismanaged. This data is recognized by studies of Siddons and his colleagues (1) and Wigley and his associates as well as a number of more current studies (2,3,4). Because of this, when the diagnosis is ultimately made, unfortunately, the bulk of patients already have well advanced disease, leading to greater health care burden, greater morbidity and earlier mortality(5).

Educational Gap/Needs Assessment
There are significant educational gaps that exist with the responders, primary care providers. A high index of suspicion for this disease goes miles in affording these patients better outcomes, reduced hospitalizations, improved exercise tolerance, and improved survival. This ability to recognize these patients arises as providers are afforded a sound fundamental working understanding of high risk groups, the preliminary work up, and the necessity of referring the patient to centers of excellence for diagnosis and management of this challenging and mortal disease, and an understanding of the variety of medical interventions available to these patients with PAH. The multiple medications and combination regimens in this arena demand an expert understanding of this disease entity, and with that, sound experience with the nuanced approaches and pitfalls in managing this complex disease, and its concomitant co-morbid diseases.

There is a need to provide a sound basic understanding of PAH to the general practitioner, physician extender, and the subspecialist alike.(6) This will benefit their patient populations in reducing evident education gaps, and improving outcomes in the high risk populations for PAH that disproportionately affect segments of the African diaspora.

References:
1. ERJ 2002 p.288
6. NMA FM Practitioner survey on PAH 2016

Intended Audience
This program is intended for primary care and family medicine physicians, endocrinologists, internists, nurse practitioners and other healthcare professionals interested in PAH.

Objectives
Upon completion of this session, participants should be able to:

1. Accurately diagnose patients through comprehensive screening and early recognition of symptoms.
2. Evaluate the patient’s condition and prescribe long-term optimal management, including knowing when and how to treat and when to consult with colleagues at an established PAH center.
3. Discuss the definition/classification of pulmonary hypertension and pulmonary arterial hypertension and the diagnostic evaluation for this disease as delineated by the American College of Chest Physicians.
4. Discuss the disproportionate high risk populations among African Americans at risk for PAH, in particular its relationship to connective tissue disease, scleroderma, portal hypertension, and HIV.
5. Delineate the different targets of therapy in PAH.
6. Analyze the treatment options, efficacy and safety of medications available for the management of PAH.
7. Describe system barriers encountered in practice as it relates to PAH and how to remedy them.

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MONDAY, AUGUST 1, 2016

1:00 – 1:20
Registration and Luncheon

1:20 – 1:40
Introduction and Program Overview / Pre-Test
Moderator
Warren A. Jones, M.D.
Endowed Chair in Health Disparities Research
Dillard University
New Orleans, Louisiana

1:40 – 2:05
Challenges in PAH Diagnosis and Classification
Octavius Polk, M.D.
Assistant Professor of Medicine
Division of Pulmonary Diseases
Howard University College of Medicine
Washington, District of Columbia

2:05 – 2:10
Audience Interaction/Questions and Answers

2:10 – 2:35
Navigating Treatment Options in Pulmonary Artery Hypertension: Current and Future Approaches in the Treatment of the PAH Patient
Leslie Kingslow, M.D.
Adjunct Faculty
Division of Pulmonary Medicine
Washington Hospital Center
Washington, District of Columbia

2:35 – 2:40
Audience Interaction/Questions and Answers

2:40 – 3:05
Pulmonary Hypertension and the African American Patient: Considerations in Sickle Cell, Scleroderma and Liver Disease
Alem Mehari, M.D.
Assistant Professor of Medicine
Division of Pulmonary Diseases
Howard University College of Medicine
Washington, District of Columbia

3:05 – 3:10
Audience Interaction/Questions and Answers

3:10 – 3:20
Panel Discussion/Post-Test/Audience Interaction with Faculty
Warren A. Jones, M.D.
Leslie Kingslow, M.D.
Alem Mehari, M.D.
Octavius Polk, M.D.
Warren A. Jones, M.D., a family physician and retired Captain in the U.S. Navy, is the Endowed Chair of Health Disparities Research and Professor of Chemistry at Dillard University in New Orleans, LA. He was most recently the Director of Healthcare Quality and Disparities at Provider Resources, Inc. He was the founding Executive Director of the Mississippi Institute for Improvement of Geographic Minority Health at the University of Mississippi Medical Center where he is a Professor Emeritus of Family Medicine and has also been a Distinguished Professor of Health Policy, Professor of Family Medicine and a Professor of Anesthesiology. He is a previous Associate Vice Chancellor for Multicultural Affairs at the University of Mississippi and past Director of the Mississippi Area Health Education Centers (AHEC).

He was previously the Executive Director of Mississippi’s Medicaid Program and a Cabinet member in the Office of the Governor of Mississippi. The Medicaid program provided services for 25% Mississippi’s total population. He currently serves on the congressionally Mandated Advisory Committee on Disability Compensation for the Veterans Administration. He has also served on the congressionally mandated Council of Councils at the National Institutes of Health (NIH). He has also served as Chair Designee of the National Advisory Council to the NIH’s National Institute on Minority Health and Health Disparities (NIMHD). He has served on the Emergency Medical Treatment and Labor Act (EMTALA) Technical Advisory Group (TAG) to the Secretary of Health and Human Services and on the National Commission for Prevention Priorities. He has completed his service on the Advisory Panel on Outreach and Education for the Centers for Medicare and Medicaid Services. He also has served on the Board of Trustees for his Alma Mater, Dillard University in New Orleans, LA. He currently serves as a Trustee at St. Andrews Episcopal School in Ridgeland, MS. He has served as Chair of the Board of Directors for the American Health Information Management Association Foundation (AHIMA) and serves on the Board of the Diabetes Foundation of Mississippi.

Dr. Jones is a past President of the American Academy of Family Physicians, an 118,300-member primary care specialty society. He has also served Chair of the AAFP’s Board of Directors and President-elect of the Academy. He is the Chair Emeritus of the Family Medicine Section of the National Medical Association (NMA). He has also served as Chair of the Maternal Child Council, Past Chair of the Family Medicine Section and Aerospace & Military Medicine Section of the NMA. He currently serves on the National Commission on Prevention Priorities and on the Board of the National Forum for Heart Disease & Stroke Prevention. He also served on the Minority Affairs Governing Council for the American Medical Association (AMA). He was most recently a Co-Lead for the Behavioral Health Subgroup of the Eunice Kennedy Shriver-National Institute of Child Health and Human Development Visioning Project.
Jones retired from the United States Navy and his position as the Senior Medical Director of the over 10 million member TRICARE Military Health Program, the military’s health insurance program in 2001. He previously served as Director of Medical and Clinical services for the Pacific region of TRICARE coordinating care for U.S. service members and their families from Alaska to Madagascar.

Jones has served on the President’s Select Panel on Surviving and Living after Cancer, the Chiropractic Implementation Committee for the U.S. Secretary of Veterans Affairs and on the Secretary’s Chiropractic Advisory Committee. In addition, Jones was a member of the Expert Panel for the Medicaid Disease Management Initiative for the Center for Health Care Strategies, the Robert Wood Johnson Foundation and the Kaiser Permanente Foundation. He was a member of the Key Stakeholders Advisory Board to the Evidence Based Research Center for the Agency for Healthcare Research and Quality (AHRQ). He is currently a member of the Board of Directors of the Mississippi Diabetes Foundation and has previously served on the Board of the National Health Council and the National Advisory Council to Rewarding Results, an advisory panel to the Robert Wood Johnson Foundation and the California Health Foundation which led to the development of the Pay for Performance initiative in health care. He is also a member of the expert panel for the Innovations in Prevention Awards, sponsored by Health and Human Services Secretary, Tommy Thompson.

Jones received his undergraduate degree in chemistry from Dillard University in New Orleans. He received his medical degree from Louisiana State University School of Medicine in 1978, and completed a family medicine residency at the Naval Hospital in Pensacola, Florida. Jones also earned a fellowship in Adolescent Medicine at the Naval Hospital in San Diego. Jones is a Fellow of the AAFP, an earned degree awarded to family physicians for distinguished service and continuing medical education.

Jones has extensive military and medical teaching experience, which includes serving as special assistant to the U.S. Navy Surgeon General and was Chair of the Department of Family Medicine at the Naval Hospital in Charleston, S.C. Jones has received numerous military honors including the Defense Superior Service Medal, and the Navy Commendation Medal for superior performance. He received the Meritorious Service Medal three times. He was recently honored as the Outstanding Black Educator in Mississippi by the Board of the Institutions of Higher Learning. He is married to the former Gennie Lacy of Pickens, MS and has six children: Aaron, Keith, Winston, Deanna, Cassandra and Madison.
Octavius Douglas Polk, Jr., M.D., serves as Clinical Assistant Professor of Medicine at Howard University College of Medicine. He is also in private practice in Washington, DC. Dr. Polk received his medical degree from the University of Mississippi, School of Medicine. He completed a residency program in internal medicine and a fellowship in pulmonary diseases at Howard University Hospital, Washington, DC. Dr. Polk completed a critical care medicine fellowship at the Maryland Institute for Emergency Medical Services Systems in Baltimore, MD. He is a Diplomate in the subspecialties of pulmonary diseases and internal medicine. He has received numerous awards, including the American College of Physicians Preceptorship Award for a Community Based Teaching Project. Dr. Polk has published several articles on pulmonary diseases. His research and scholarly activities include clinical trials via the Howard University Cancer Center, and Howard University Hospital Pulmonary Critical Care Medicine Clinical Research Projects (Active) with Residents and Fellows. Dr. Polk’s interests and clinical research activities focus on COPD/Asthma, Sarcoidosis, Lung Cancer and Smoking Cessation.
Challenges in PAH Diagnosis and Classification

O. D. Polk, Jr., MD
Assistant Professor of Medicine
Howard University College of Medicine
Washington, DC

Objectives

- Define the World Health Organization (WHO) Classifications of pulmonary hypertension.
- Identify the signs and symptoms that suggest the diagnosis of pulmonary hypertension.
- Describe the appropriate workup of a patient with possible pulmonary hypertension.

Pulmonary Circulation

- Pulmonary Vascular Bed
  - Low Resistance
  - High Capacitance
  - Pressures 15%-20% of the systemic circulation
- Normal Pulmonary Pressure
  - PA Systolic Pressure – 15-30 mmHg
  - PA Diastolic Pressure – 4-12 mmHg
  - Mean Values – 9-18 mmHg

What is Pulmonary Hypertension?

- By current definition, “pulmonary hypertension” is present when the mean pulmonary arterial pressure is ≥ 25 mmHg
- Currently classified by the World Health Organization (WHO) into 5 categories of disease
- The terms “primary” and “secondary” PH are historical. Their use is now discouraged.
5th World Symposium on PAH: Update

PAH Diagnosis
- Pulmonary Hypertension (PH) – mPAP ≥ 25 mmHg at rest
- Pulmonary Arterial Hypertension (PAH) – mPAP ≥ 25 mmHg at rest
- +PCWP (or LVEDP) ≤ 15 mmHg
- +PVR > 3 Wood Units (New)

Prevalence and Characteristics of PH

<table>
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<tr>
<th>Condition</th>
<th>Prevalence</th>
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<tr>
<td>PAH</td>
<td>15/million</td>
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<tr>
<td>IPAH</td>
<td>5.6/million</td>
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<tr>
<td>PAH-Scleroderma</td>
<td>Progressing Echocardiographic Study – 26.7% of Canadian CTD-Centers; 22% Limited and 26% Diffuse Scleroderma Patients</td>
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<td>PAH in Scleroderma Patients</td>
<td>10%</td>
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<tr>
<td>PAH in CTEPH</td>
<td>1/600 patients after first PE</td>
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<tr>
<td>PAH in CTEPH</td>
<td>3.1% at 1 year and 3.3% at 2 years</td>
</tr>
<tr>
<td>PAH in Scleroderma Patients</td>
<td>9% heart TRV ≥ 2.0 mH</td>
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<tr>
<td>PAH in Thyroid Disease</td>
<td>42% of patients with hyperthyroidism</td>
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<tr>
<td>PAH in Schistosomiasis</td>
<td>30% of cases (in 2 Brazilian PAH Centers)</td>
</tr>
<tr>
<td>PAH in Postpolycythemia</td>
<td>12.5% of PAH have had a splenectomy</td>
</tr>
</tbody>
</table>

Heritable PAH
- Autosomal dominant
- Mutations in bone morphogenetic protein receptor II (BMPR2) detected in >70% of familial PAH (also in >20% of PAH cases)
- Incomplete penetrance (20%)
- Genetic anticipation
- Mutations in actin-like kinase-type 1 (ALK1) and endoglin (ENG) associated with hereditary hemorrhagic telangiectasia can cause PAH

Note:
- Heritable PAH
- Autosomal dominant
- Mutations in bone morphogenetic protein receptor II (BMPR2) detected in >70% of familial PAH (also in >20% of PAH cases)
- Incomplete penetrance (20%)
- Genetic anticipation
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PAH Related to Connective Tissue Disease

- Connective tissue diseases
  - limited systemic sclerosis (most common) (0-2%)
  - diffuse systemic sclerosis
  - MCTD
  - systemic lupus erythematosus (5-8%)
  - Sjogren’s syndrome (rare)
  - rheumatoid arthritis (rare)
  - Inflammatory myopathies (rare)
- PAH is one of the primary causes of death in scleroderma
- Similar to IPAH pathology
- Medical treatment same as for IPAH, but benefits less than for IPAH

Incidence of CTEPH

- Approximately 3% to 4% after acute PE
- USA: 600,000 cases of acute PE each year
- Only 40% to 50% of CTEPH patients have a history of previous episodes of acute PE
- VQ scan identifies old PE better than CTA

Pathology of PAH

WHO Group 1: Characterized by progressive growth and vasoconstriction of small pulmonary arteries

PAH: Hemodynamic and Clinical Course

Time

PAH: Hemodynamic and Clinical Course

Time

PAH: Hemodynamic and Clinical Course

Time
Slide 19
Survival in PAH

Slide 20
Case #1: Rita
- 37-yr-old woman, previously healthy
- Delivered second child 14 months previously
- Limited exercise tolerance since delivery, attributed to weight gain
- Dyspnea while playing with older child; syncope while walking up an incline

Slide 21
Rita’s Initial Symptoms
- Currently has dyspnea with mild exertion, walks slowly in store
- Exertional light-headedness
- Atypical chest pain
- Occasional palpitations
- Lower extremity edema

Slide 22
Rita’s Additional History
- PMH: 2 children, 4 yr and 14 mo
  - IBS: diet-controlled
- Meds: none
- Allergies: contrast dye
- FH: CAD, DM, Htn
- SH: rare ETOH, o/w unremarkable

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What are the symptoms?
- Progressive Dyspnea
  - Initial symptom in more than half of patients with PH
  - Ultimately occurs in approximately 85%
  - 20% of patients reporting symptoms for > 2 years before a diagnosis of PAH is made
- Fatigue (26%)
- Chest Pain (22%)
- PreSyncpe/Syncpe (17%)
- Lower Extremity Edema (20%)
- Palpitations (12%)

Slide 24
What are the PE Findings?
- May be surprisingly unremarkable early in PH
- Findings of RH Strain and RH Failure
  - Elevated jugular venous pressure
  - RV pulsatile heave or subcostal heath
  - Loud P2
  - Right sided S3 or S4
  - Holosystolic TR murmur
- Peripheral Edema and/or ascites
- Hepatomegaly due to hepatic congestion

Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population

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CT appropriate when VO2 in equivocal range
Pulmonary angiogram required for moderate or high probability VO2 and pulmonary embolus considered

Slide 32

PH: The Importance of Hemodynamics
Pulmonary venous hypertension
Elevated PCWP, normal PVR

Slide 33

Rita’s Labs
- ANA: negative
- Echo: nl LV Fn, RAE, RVE, RVSP 60, TEE—no shunt
- V/Q: normal
- PFTs: nl volumes and flows, DLCO 81%
- 6MWD: 222 m, 99-96%

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In IPAH and CTEPH:
- >20% have lung volumes <80%
predicted
- DLCO mildly reduced (60-80%) predicted
- PVR correlates with reduction in DLCO

In systemic sclerosis:
- >20% have an isolated reduction in DLCO
- Severity predicts future PH
- DLCO correlates inversely with IPSS

Slide 35

17% (37/210) of patients with AH >20 have daytime mPAP >20 mm Hg
- 16 had mPAP >25 mm Hg; only 2 had mPAP >35 mm Hg
- Marked ↑ with sub-max exercise (mean mPAP 42 mm Hg) — in part due to ↑ PCWP
- Contributing factors: obesity, hypoxemia, COPD

In patients with OSA, ↓PAP reported in response to CPAP therapy

Untreated – response to other treatment likely less effective

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Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population
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Slide 37

Rita: Right Heart Cath

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<th>1/29/13 Baseline</th>
<th>Nitric Oxide 20 ppm</th>
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</thead>
<tbody>
<tr>
<td>RAP (mm Hg)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>93/40, mean 63</td>
<td>93/46, mean 64</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>10</td>
<td></td>
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<tr>
<td>Oxygen saturation (%)</td>
<td>52.9</td>
<td>58.3</td>
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<tr>
<td>Pulmonary artery Femoral artery</td>
<td>91.4</td>
<td>91.7</td>
</tr>
<tr>
<td>Cardiac output / Cardiac index (L/min) Fick</td>
<td>2.3/1.3</td>
<td>2.88/1.52</td>
</tr>
<tr>
<td>PVR (Wood units) Fick</td>
<td>21.2</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Slide 38

- Oxygen saturations (SVC, IVC, PA, 5A)
- Right atrial pressure
- RV systolic and end-diastolic pressure
- PA systolic, diastolic, and mean pressure
- PAPV, LVEDP, or LAP
- Thermodilution rather than Fick CO, CI
- Pulmonary vascular resistance
- Systemic systolic, diastolic, and mean pressure
- Heart rate
- Vasoconstrictor response

Fluid challenge to assess for HHF (500mL)

- Rate 100 bpm
- Initial D-5 normal saline
- 1 ml/kg/hr
- Monitor fluid status and response
- Repeat if response inadequate

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Importance of Right Heart Cath

- PVR
- TPG
- LVEDP
- LAP
- Pulmonary Hypertension
- PAH
- PVH
- PBF
- LV dysfunction
- V/Q mismatch
- UH disease
- PV obstruction
- PH
- PAH
- PVH
- PBF

Slide 40

Who should be screened for PH?

- Patients with
  - Systemic Sclerosis
  - Family history of a heritable form of PAH
  - Patients with portal hypertension being considered for organ transplantation
- Optimal screening interval has not been adequately studied
- Annual screening has been recommended


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NICE PAH Diagnostic Algorithm

- Symptoms, signs, history suggestive of PAH
- Ethanolamine papulosa with 20 mg
- History: signs, risk factors, ECG, Key
- PAPV and BiPAP, consider BiO2, with PAH
- PVR 
- Systolic or diastolic hypertensive disease
- Signs of severe PAH/IV infusion
- Referral to the expert center
- VQ scan
- Inferior pulmonary embolus detected
- Referral to the expert center
- Tricuspid regurgitation
- Faster gradient for carbon monoxide

Summary

- High index of suspicion
- Thorough diagnostic evaluation
- Exclude thromboembolic disease
- Evaluate potential causes/contributing issues
- Right heart catheterization required prior to initiating PAH therapy
- Baseline functional evaluation
Leslie W. Kingslow, M.D. is a proud third generation physician originally from Orange, New Jersey. He completed his undergraduate training at the University of Virginia in Charlottesville, Virginia. He received his medical degree from Howard University College of Medicine in Washington, D.C. in 1988, and completed his residency in Internal Medicine in 1991 at the Virginia Commonwealth University. Dr. Kingslow completed his fellowship in Pulmonary and Critical Care Medicine at the George Washington University Hospital in Washington, DC in 1996, after which he joined Pulmonary Critical Care Associates, PC, of Washington, DC, where he has maintained a partnership for the last 20 years, and has developed expertise in the areas of pulmonary vascular diseases, sarcoidosis, emphysema, asthma, and long term mechanical ventilation management. He has held adjunct faculty positions in the Pulmonary and Critical Care Fellowship training programs at the Washington Veteran’s Administration Hospital, and Howard University Hospital, respectively, and currently remains as adjunct faculty in the Division of Pulmonary Medicine and Critical Care at Washington Hospital Center, Washington, DC. Dr. Kingslow is recognized as a regional, national and international speaker on a variety of pulmonary disease states and health disparities.

Currently, Dr. Kingslow maintains active medical staff positions at Washington Hospital Center, Providence Hospital, and the Bridgepoint Hospital of Washington. In 2009, Dr. Kingslow established a pulmonary-critical care medicine service at Schneider Regional Medical Center in St. Thomas, USVI. Under his directorship, it has provided pulmonary services to the residents of St. Thomas and surrounding islands for seven years. Dr. Kingslow is a member of numerous professional organizations, and a fellow of the American College of Chest Physicians, a member of the American College of Physicians, and the National Medical Association. He sits on the Medical Advisory Board for Gilead Pharmaceuticals and United Therapeutics. He has sat on a variety of boards, including Global Health Connections International, Adventures in Health Education and Agriculture (AHEAD, Inc), the Howard University Medical Alumni Association, and is a member of a variety of civic and social organizations.
Navigating Treatment Options in Pulmonary Artery Hypertension: Current and Future Approaches in the Treatment of the PAH Patient

Leslie W. Kingslow, MD, FCCP
Adjunct Faculty
Medstar, Washington Hospital Center
Washington, DC

Slide 1

Slide 2

Disclosures

- Current member of Advisory Board / Speakers Bureau for:
  - United Therapeutics
  - Gilead

Slide 3

Slide 4

PULMONARY HYPERTENSION
CELEBRITY STORIES:
NATALIE COLE
PULMONARYHYPERTENSIONSTORIES.COM

Slide 5

Slide 6

Survival in Primary PAH: NIH Registry

* Estimated median survival 2.8 years

<table>
<thead>
<tr>
<th>Predictors of survival in PAH</th>
<th>Mean Pulmonary artery pressure</th>
<th>Mean right atrial pressure</th>
<th>Mean cardiac index</th>
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<td>Predictors</td>
<td>Mean (mm Hg)</td>
<td>Mean (mm Hg)</td>
<td>Mean (L/min/m²)</td>
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<td>&lt;25</td>
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<td>&gt;95</td>
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Estimated mean survival time, months

- 48
- 46
- 1
- 43
- 17

Evolution of PAH Therapy

<table>
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<tr>
<th>Year</th>
<th>PDE5 Inhibitors</th>
<th>PAH</th>
<th>PAH + Calciolytic</th>
<th>Candesartan</th>
<th>Other PAH Therapies</th>
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<td>2011</td>
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<tr>
<td>2012</td>
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<td>Inhaled Nitric Oxide</td>
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<td>2013</td>
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<td>Inhaled Nitric Oxide</td>
<td>Inhaled Nitric Oxide</td>
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<td>2014</td>
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<td>Inhaled Nitric Oxide</td>
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</tr>
</tbody>
</table>

Leslie Kingslow, M.D.
Leslie Kingslow, M.D.
Current Treatment Options for PAH

- Hemodynamics (with/without vasopressors)
- Exercise tolerance
- Right heart catheterization
  - Pulmonary hypertension
  - Pulmonary vascular resistance
  - Pulmonary artery pressure
  - Systemic to pulmonary shunt

Treatment decisions are based on risk stratification, NYHA Functional Class, prior treatment status, response to CCBs, and mode of administration (IV and SQ, prostanoids administration are most difficult)

Sakamoto, JS Chest, 2014; 146:211-49

Approved Therapeutic Targets for PAH

- Endothelin Pathway
- Nitric Oxide Pathway
- Prostacyclin Pathway
- Endothelial cells
- NO synthase
- cGMP
- Nitric oxide
- Prostacyclin
- Endothelin-1
- smooth muscle cells

Survival among Patients With IPAH: Epoprostenol vs Conventional Therapy

THE HISTORIC GOLD STANDARD FOR PAH RX

Week 13 EFFICACY Results

- **Riociguat** (n=254)
- **Placebo** (n=236)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riociguat</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change in 6-MW distance (m)</td>
<td>+30</td>
<td>-6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Mean Change in PVR (dynes-cm⁻²)</td>
<td>-228</td>
<td>-9</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>NT-ProBNP (pg/mL)</td>
<td>-232</td>
<td>-238</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Borg Dyspnea score</td>
<td>-0.4</td>
<td>+1.0</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>Improvement in Time to Clinical Worsening</td>
<td>+</td>
<td></td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Improvement in WHO FC</td>
<td>+</td>
<td></td>
<td>p = 0.003</td>
</tr>
</tbody>
</table>

Hindert M et al. (J Hypertens. 2012;30:585-593)
Leslie Kingslow, M.D.

Slide 19

<table>
<thead>
<tr>
<th>Week 12 (Tf) Results</th>
<th>Riociguat (n=256)</th>
<th>Placebo (n=126)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change in 6MWD distance [m]</td>
<td>+36</td>
<td>-6</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Mean Change in PVR (dynes-cm$^{-5}$)</td>
<td>-226</td>
<td>+23</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>NT-Pro-BNP</td>
<td>-291</td>
<td>+76</td>
<td>$p &lt; 0.001$</td>
</tr>
<tr>
<td>Borg Dyspnea score</td>
<td>0.8</td>
<td>0.2</td>
<td>$p = 0.003$</td>
</tr>
<tr>
<td>Improvement in time to clinical worsening</td>
<td>none</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Improvement in WHO FC</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Riociguat is indicated for those CTEPH patients who are inoperable or have residual thrombus in the PA following pulmonary endarterectomy.

Slide 20

**Case Study 1**

- 28 year female treated by PCP for asthma for last 9 months
- Began having palpitations and dizziness with stair climbing and was referred to cardiologist
- ECHOcardiogram, Holter monitor, exercise ECG and V/Q scan
- Based on her ECHO results, she underwent a left and right heart catheterization 2 months ago and was found to have PAH.
- She was placed on sildenafil by her cardiologist and referred to our office for an initial consultation.

Slide 21

**Case Study 1 (cont)**

<table>
<thead>
<tr>
<th>WHO</th>
<th>FC II (2/18)</th>
<th>FC II (4/18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>BP 130/101, Pulse 101</td>
<td>BP 134/92, Pulse 100</td>
</tr>
<tr>
<td></td>
<td>Systolic murmur of TR, Paroxysmal RV heave</td>
<td>RV heave, bx 82, gr II/IV murmur</td>
</tr>
<tr>
<td>ECHO</td>
<td>RV press overload with mild TR, Mild RV, Mild RAE, Ext. RVSP 78 mm Hg</td>
<td>Essentially unchanged</td>
</tr>
<tr>
<td>6 min Walk Distance</td>
<td>420 meters</td>
<td>440 meters</td>
</tr>
<tr>
<td>Right Heart Cath</td>
<td>RA 8 mmHg, PA 48</td>
<td>RVSP 95</td>
</tr>
<tr>
<td>Treatment</td>
<td>Initiated on Sildenafil</td>
<td></td>
</tr>
</tbody>
</table>

Slide 22

**Case Study 1**

- 2 months after diagnosis and initiation of sildenafil the patient is limited due to exertional dyspnea associated with exercise.
- Her job requires a lot of walking.
- She had some limited improvement with sildenafil initiation, however, now she feels about the same as she did before treatment.
- 6 min walk distance improved from 420 to 440 meters.
- What are the treatment options for this fairly typical patient with PAH?

Slide 23

**An Evolving Paradigm**

*From Sequential to Initial Upright Combination Therapy*

- Sequential Combination
  - Drug 1
- Upright Combination
  - 2 or 3 Drugs
- Impact on Outcomes


Slide 24

- Today, monotherapy is not sufficient any more for the management of Pulmonary Arterial Hypertension (PAH).
Risk Stratification
- Based on estimated annual mortality rate
  - Low risk (< 5%)
  - Intermediate risk (5% – 10%)
  - High risk (> 10%)
- Identification of risk based on 3 domains
  - Symptoms
  - Exercise capacity
  - RV function
- Potential overlaps in categories

PAH Treatment Goals
- Prevention of clinical worsening/disease progression
- Improved survival
- Improved quality of life
- Improved exercise capacity/Improve FC to I
- Maintain good RV function/Improved hemodynamics

Seraphin
- Treatment naïve (36.2%) or on background therapy (63.7%)
  - PDE5
  - Oral or inhaled prostanoid
  - Other
- Stable Patients
  - Mostly FC II or III
  - Considered sufficiently treated according to previous goal oriented treatment strategies
- Primary endpoint: Morbidity / mortality, including atrial septostomy, lung transplant, initiation of IV/SQ prostanoids, or hospitalization

Primary Endpoint in Pretreated Patients

Primary Endpoint

Combination Therapy Options for PAH

Integrating GLP-1 Inhibitors Into a Comprehensive Diabetes Care Management Regimen - The Incretin Experience
Slide 31

1-yr Survival Estimates in the Subsequent Year by Change in REVEAL Score

<table>
<thead>
<tr>
<th>Change in Risk Score</th>
<th>Survival, %</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased (improved)</td>
<td>93.7 +/- 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unchanged</td>
<td>90.3 +/- 1.0</td>
<td>---</td>
</tr>
<tr>
<td>Increased (worsened)</td>
<td>84.6 +/- 1.3</td>
<td>---</td>
</tr>
</tbody>
</table>


Slide 32

Case Study #2

- 45 yo female, 5 year history of SSC disease referred with newly diagnosed PAH by RHC.
- PCP previously screened her with echocardiograms annually that were interpreted as normal and unchanged.
- Her exercise tolerance recently declined.
- Due to high risk for PAH in the setting of SSC the patient was referred for a RHC.
- Diagnosed with PAH in 2015.

---

Slide 33

Case Study #2

- FC II
- 6 min walk distance 370 meters
- PE: BP 140/75 pulse 82 and unremarkable
- ECHO: Mild RAE, mild TR, estimated RVSP 50mmHg + CVP, normal LV function
- RHC
  - RA 5 mmHg, PAPm 29 mmHg, PCWP 5 mmHg, CI 2.7 L/min/m², PVR 4.9 WU, SVO2 71

---

Slide 34

Rationale for Combination Therapy

- Several pathways involved in pathophysiology
- Potential for synergistic effect
- Severe nature of this disease
- Successfully used in heart failure, HIV infection...

Combination therapy

Sequential (add-on) or Up front (first-line)?

---

Slide 35

Approved Therapeutic Targets for PAH

---

Slide 36

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION)

AMEBITION Study (NCT00359844)

AMBITION Trial Dosing

<table>
<thead>
<tr>
<th>Day</th>
<th>Letera</th>
<th>tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>After Week 4, increase dose of tadalafil</td>
<td>Letera 10 mg, tadalafil 40 mg</td>
<td></td>
</tr>
<tr>
<td>After Week 8, increase dose of Letera</td>
<td>Letera 15 mg, tadalafil 40 mg</td>
<td></td>
</tr>
</tbody>
</table>

EVENT DRIVEN STUDY

- Annual PPH and HR and RV 39.75 yoe, 2.2 transformation
- Study completed after 110 primary end points event:
  - History and patient 60 days to delirium ruleout
  - Clinical stability: First occurrence of death, hospitalization for worsening PAH, short-term clinical worsening or hospitalization for long-term clinical worsening.
**Slide 37**

**Initial Use of Ambisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION)**

- Combo reduced risk of disease progression by:
  - 49% compared to Letaris mono
  - 45% compared to Tadalafil mono

---

**Slide 38**

**Initial Use of Ambisentan plus Tadalafil in Pulmonary Arterial Hypertension (AMBITION)**

- Reduced risk for disease progression
- Reduced hospitalizations for worsening PAH
- Improved exercise tolerance
- Greater reductions from baseline in NT-pro-BNP
- Higher clinical satisfactory response
- Greater 6mW distance (43m vs 23m and 22m)
- Class I level B recommendation for WHO Group I FC II and III PAH

---

**Slide 39**

**Approved Therapeutic Targets**

![Diagram showing approved therapeutic targets]

---

**Slide 40**

**Selexipag: Prostanoid-Like**

- Orally active IP agonist
- Highly selective for IP receptor, distinguishing it from other prostanoid receptor agonists
- Early data reflected improvement in PVR
- Adverse events reduce over time with continued dosing

---

**Slide 41**

**GRIPHON: Selexipag for the Treatment of PAH**

- Multi-center, double-blinded, placebo-controlled, parallel group
- Assessed long term safety and efficacy of Selexipag in PAH
- Clinical relevant and highly robust clinical end point:
  - Time to first morbidity or mortality event up to the end of the double blinded treatment phase
  - At baseline, 20% treatment naïve, 80% were on PDE5 inhibitor and/or ERA
  - Mean duration of Rx 76 and 71 weeks
  - Selexipag 200mg to 3600 mg PO BID

---

**Slide 42**

**GRIPHON: Selexipag for the Treatment of PAH**

- 360 points: Hazard ratio 0.65
- 40% reduction in morbidity/mortality rate in 64 arm @ 26 weeks
- Hazard ratio 0.65
- 95% CI 0.46 to 0.73
- P=0.001 (one-sided log rank test)

---
Leslie Kingslow, M.D.

Slide 43
Collaborative Care With PH Centers

- Primary Care Pulmonary
- Local Care Pulmonary
- Rheumatology Cardiology
- Specialty Pharmacy/ Specialty Nurse
- Pulm HTN Association/ Support Grps

Slide 44
Future Direction for PAH
- 3-D computer modeling of pulmonary vasculature and RV
- INOpulse delivery system pulsatile inhaled nitric oxide.
- Pharmacogenomics
- Targeting inflammation
- Epigenetics/apoptosis—cancer lessons applied to PAH
- Endothelial progenitor cells
- Cardiac regeneration/angiogenesis
- Animal models

Slide 45
Summary
- The treatment for patients with PAH is based on initial evaluation and risk assessment.
- Treatment should be delivered by clinicians with expertise in this area, preferably at a PAH specialty center.
- Ongoing monitoring of response to therapy and risk reassessment is critical.
- There is a growing armamentarium of therapeutic strategies to modify treatment, particularly with upfront combination/multidrug therapy as supported by REVEAL data and recent pivotal studies, and for patients who are worsening despite current therapy.

Slide 46
Navigating Treatment Options in Pulmonary Artery Hypertension
Current and Future Approaches in the Treatment of the PAH Patient
Leslie W. Kingslow, MD, FCCP

THANK YOU!!
Alem Mehari, M.D. is an Assistant Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at Howard University College of Medicine. She is certified by the American Board of Internal Medicine and has a Subspecialty Certification by the American Board of Pulmonary Medicine. After completing her medical education in Ethiopia, she interned in Internal Medicine at Howard University College of Medicine, where she completed her residency in 2006.

After functioning as an Emergency Medicine Physician at Washington Veteran's Affairs Hospital for one year, Dr. Mehari joined a fellowship in Pulmonary Medicine at Howard University. Upon successful completion of her fellowship in Pulmonary Medicine, Dr. Mehari completed a two-year postdoctoral research fellowship in pulmonary vascular disease at the National Heart, Lung and Blood Institute (NHLBI) where she studied pulmonary vascular diseases with special emphasis on pulmonary vascular complications of sickle cell disease. This was a highly productive experience resulting in three manuscripts in top peer-review journals including JAMA.

Upon successful completion of fellowship at the NIH, Dr. Mehari joined the faculty at Howard University College of Medicine where she established a Pulmonary Hypertension Center of Excellence. Dr. Mehari also functions as a key clinical faculty and research mentor to the pulmonary fellows as well as residents in the internal medicine residency program, and medical students who have a key interest in research. Also since joining the faculty at Howard in 2011, Dr. Mehari has maintained a productive research program (17 additional manuscripts and 30 abstracts). Furthermore, she has begun to receive national recognition for her research accomplishments.

Dr. Mehari is a member of numerous professional organizations, including the American College of Physicians, American Thoracic Society, and the Pulmonary Hypertension Association.
Alem Mehari, M.D.

**Slide 7**

**Prevalence and Prognosis of Pulmonary Hypertension in Sickle Cell Disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Prevalence of PH (%)</th>
<th>Mortality in PH patients</th>
<th>Mortality in patients without PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gladstone et al</td>
<td>115</td>
<td>34</td>
<td>12% at 48 months</td>
<td>2% at 48 months</td>
</tr>
<tr>
<td>Banzo et al</td>
<td>124</td>
<td>25</td>
<td>27% at 30 months</td>
<td>7% at 30 months</td>
</tr>
<tr>
<td>Alegre et al</td>
<td>76</td>
<td>48</td>
<td>12% at 24 months</td>
<td>16% at 24 months</td>
</tr>
<tr>
<td>Masin et al</td>
<td>101</td>
<td>23</td>
<td>62% at 60 months</td>
<td>30% at 60 months</td>
</tr>
</tbody>
</table>

**Slide 8**

**Limitations of Echocardiography in Diagnosing PH**

- Variability in results
- TRV is increased by pain crisis
- By technician or echocardiographer
- High false positive in SCD
- Echo is not adequate to diagnose PH in an individual patient or to guide therapy
- Does not distinguish Hemodynamic subtypes

**Slide 9**

**CMR predictors of mortality in patients with sickle cell disease**

**Slide 10**

**Reduced RV Function Associated With Poor Outcome Regardless of PVR**

**Slide 11**

**Case History: KB (1975 – 2010)**

- Sickle Cell Anemia
- Recurrent pain crisis
- Priapism
- Pulmonary hypertension
  - Right Heart Catheterization results:
    - mPAP=44mmHg
    - PAOP=12mmHg
    - CO=12.8 L/min
    - TPG=22mmHg
    - PVR=2.6 Wood Units

**Slide 12**

**Sudden Death**

At home, watching TV with his mother
- Went upstairs to his bedroom
- His mother heard him walking, then fell
- “I knew he was dead.”
- Mother consented to autopsy
Alem Mehari, M.D.

Slide 13: Lung Blood Vessels in SCD PH
- Narrowed, restricted luminal capacity

Slide 14: Images of Pulmonary Hypertension

Slide 15: Pathologic Changes

Slide 16: Major Causes of Death in Patients With PAH
- Pulmonary Hypertension (PAH)
- Sudden Death
- Unknown
- Sepsis

Slide 17: First Case Series of RHC in SCD
- Pulmonary Hypertension and Cor Pulmonale in the Sickle Hemoglobinopathies

Slide 18: First Case Series of RHC in SCD with Autopsy

Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population
**OBJECTIVES**

- To characterize the hemodynamic phenotypes using highly rigorous standards.
- To identify the clinical correlates of SCD-PH
- To estimate expected survival of patients with SCD-PH
- To identify the hemodynamic predictors of mortality
- To identify the clinical correlates of SCD-PH

**RESULTS:**

### Hemodynamic Characteristics in SCD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PH (n=168)</th>
<th>No-PH (n=235)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP</td>
<td>36 ± 9</td>
<td>19 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAP</td>
<td>10 ± 5</td>
<td>6 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAWP</td>
<td>16 ± 5</td>
<td>12 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPG</td>
<td>21 ± 10</td>
<td>8 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO</td>
<td>8 ± 3</td>
<td>9 ± 2</td>
<td>0.15</td>
</tr>
<tr>
<td>PVR</td>
<td>226 ± 149</td>
<td>74 ± 38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population

Alem Mehari, M.D.

Slide 25
Figure 1: Schematic Diagram of study population

Slide 26
PH and Early Mortality in SCD

Slide 27
Hemodynamic Mortality Predictors in Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPAP, per 10 mmHg</td>
<td>1.80 (1.15–2.80)</td>
<td>0.009</td>
</tr>
<tr>
<td>PP, per 10 mmHg</td>
<td>2.14 (1.19–3.85)</td>
<td>0.011</td>
</tr>
<tr>
<td>mPAP, per 10 mmHg</td>
<td>2.11 (1.06–4.19)</td>
<td>0.032</td>
</tr>
<tr>
<td>TP, per 10 mmHg</td>
<td>2.06 (1.04–4.08)</td>
<td>0.038</td>
</tr>
<tr>
<td>PVR, per Wood unit</td>
<td>1.62 (1.10–2.37)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Slide 28
Mortality Predictors

Slide 29
Diagnostic Evaluation of PH in SCD

Slide 30
Summary
- PH measured by RHC occurs in 6-10% adults with SCD associated with high mortality
- Acute increases in pulmonary artery pressure occur in the ACS and VOC and in the presence of PH can lead to acute right ventricular failure and sudden death
- PVH and PAH both occur in SCD adults
- Hemodynamic indicators of PAH severity predict mortality.
- Five-year survival remains unacceptably high at 64%.
**Future Directions**

- To date there is limited data in efficacy and safety of PAH targeted therapy in SCD
- Clinical trials that focus identifying underlying pathobiology and effective therapy of SCD-PH coming from well hemodynamically characterized patients are urgently needed

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**Pulmonary Hypertension in Connective tissue Diseases**

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**PAH Related to Connective Tissue Disease**

- Connective tissue diseases
  - limited scleroderma (most common)
  - diffuse scleroderma
  - systemic lupus erythematosus
  - Sjogren’s syndrome
  - rheumatoid arthritis
  - MCTD
- PH is one of the top causes of death in scleroderma
- Similar to IPAH pathiology
- Medical treatment same as for IPAH, but benefits less than for IPAH

---

**Changing Patterns of Mortality in Scleroderma**

---

**Types of PH In Scleroderma**
Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population

Slide 43

1-Year Mortality After Hospitalization for PAH-Related Right Heart Failure

Slide 44

Why is SSc-PH/PAH so Difficult to Treat?
- Older Patients
- Interstitial Lung Disease
- LV Diastolic Dysfunction
- RV Diastolic Dysfunction
- More severe structural vasculopathy
- Outcome measures may be inappropriate
- Poor recognition in the community

Slide 45

Predictors of Mortality in SSc-PAH From the REVEAL Registry: 3-Year Follow-up

Slide 46

Summary
- PAH secondary to connective tissue disorders is a cause of substantial morbidity and mortality
- Patients with systemic sclerosis are at risk of developing PH/PAH over time
- Survival of patients with PAH secondary to connective tissue disorders is not as good compared with PAH due to other etiologies
- Early diagnosis and treatment is extremely important

Slide 47

Pulmonary Vascular Consequences of Hepatic Dysfunction

Slide 48

Portopulmonary Hypertension
- Prevalence overall: 2-5% by RHC; liver transplant candidate: 4% to 17%
- Dependent on portal HTN, not hepatocellular dysfunction
- Poor prognosis: higher risk of death than IPAH pts
- Liver transplant
  - may improve survival with mild to moderate PAH (25-50%, 5 yr)
  - significant PAH (mPAP >36 mm Hg) predicts unacceptably high perioperative mortality

Alem Mehari, M.D.
Alem Mehari, M.D.

Slide 49

REVEAL: Variables Associated With Increased Mortality

Hazard Ratio 1-Year Mortality

- Pulmonary Hypertension
- Family History
- Male Sex
- NYHA Class IV
- PVR >52
gg

Slide 50

Multivariate Analysis of Risk Factors for Portopulmonary Hypertension (PoPH)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>2.00</td>
<td>1.00-4.00</td>
<td>0.045</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>4.02</td>
<td>1.00-16.18</td>
<td>0.048</td>
</tr>
<tr>
<td>Hepatitis C infectiona</td>
<td>0.36</td>
<td>0.09-1.32</td>
<td>0.16</td>
</tr>
</tbody>
</table>

N=538 patients evaluated for PoPH in 91 US centers between 2003 and 2005.
Note: Reduced risk of PoPH, Hepatitis C infection did not alter risk of PoPH.
(Revised 7/26, updated: 2005-04-15)

Slide 51

Portopulmonary Hypertension: RHC to Distinguish Hemodynamic Subsets

- Normal
  - Volume overload: normal PVR
    - PA mean >25 mm Hg, PCW >15, PVR normal
  - High output: normal PVR
    - PA mean >25 mm Hg, CO >4, PVR normal
  - Portopulmonary hypertension: PVR >3
    - PA mean >25 mm Hg, PCW >15, PVR >3

Slide 52

With success of orthotopic liver transplantation (OLT)

- Liver – lung relationships more than academic interest
- 6,000 OLT/yr; 18,000 pts on waiting lists
- 5% have clinically significant lung problems that may affect OLT survival

Slide 53

POPH in OLT Era

Liver Transplant 2004, 10:174-182
- 30 (45%) denied OLT due to severity of POPH
  - MPAP = 53 mmHg
  - PVR = 814 dynes/s/cm²
- 36 (55%) had OLT (13 died - 30% mortality)
  - 5 died during transplant surgery
  - 2 died during transplant hospitalization (within 18 days of transplant)
- If MPAP > 35 mm Hg, mortality 66%
- only 1/3 had proangiogenesis therapy pre-OLT

Slide 54

AASLD practice guidelines: Evaluation of the patient for liver transplantation (POPH)

- Hepatology 2005; 41:1407-1432

Recommendation
- All patients undergoing evaluation for portal vein thrombosis should undergo screening for pulmonary hypertension (PH).
- Doppler ultrasonography is an excellent screening test in this setting, however, patients and results should be confirmed with right heart catheterization (RHC).
- Patients with severe pulmonary hypertension should not consider liver transplantation until the condition is effectively controlled with medical therapy.
POPH Summary

- POPH uncommon, but serious
- Screen by transthoracic echocardiography
- Confirm by right heart catheterization
- Medical treatments evolving
  - Liver transplantation can be done in carefully selected patients
  - But long-term outcomes are to be defined
  - Cure vs control of POPH?
Update on the Management of Pulmonary Arterial Hypertension in the Underserved Population

LUNCHEON SYMPOSIUM

Monday, August 1, 2016
1:00 p.m. – 3:20 p.m.
Los Angeles Convention Center
Room 408A
Los Angeles, California

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