# Management of Post-Transplant Complications for Non-Transplant Centers

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# Speaker Disclosures:

- None to disclose
- The speaker will only discuss adult implications
- The speaker will not speak to off label use of medications

# Pulmonary Hypertension

- Basic definition : High blood pressure in the lungs

- Has several subsets to more precisely define PH:
  - Pulmonary Artery Hypertension (PAH)
  - Non-Pulmonary Artery Hypertension

# Pulmonary Hypertension: Epidemiology

- PH as a whole is difficult to determine exact prevalence d/t associated with many diseases/syndromes[1]
- About 200,000 hospitalizations/per as either primary or secondary diagnosis in USA[1]
- Approximately 15,000 deaths attributed to PH, but this is thought to be underestimated[1]

# Pulmonary Hypertension: Epidemiology

- Risk Factors:
  - Schistosomiasis (parasitic infection)
  - Living in high altitudes
  - Sickle Cell Disease

# Pulmonary Hypertension: Epidemiology

- Expense:
  - PAH related health care costs is approximately $214,924 per patient per year including baseline diagnosis and 12 month follow-up care[2]
  - Medication costs: $12,761 (sildenafil) - $97,615 (tresprostinil)[3]

# Pulmonary Hypertension: Pathophysiology

- Two primary pathways of PH Pathophysiology:
  - Non-Pulmonary Arterial Hypertension

    Pulmonary venous htn → Pulmonary artery htn = Damaged arteries

  - Pulmonary Arterial Hypertension

    Pulmonary artery damage → Pulmonary artery htn = Damaged arteries

- Both end with pulmonary arteries (small resistance arteries[2]) being damaged

# Pulmonary Artery Hypertension: Pathophysiology[3]

**Nitric Oxide**
- Decreased production
- Decreased platelet inhibition
- Decreased vasodilation

**Prostacyclin**
- Decreased production
- Decreased platelet inhibition
- Decreased vasodilation

**Thromboxane $A^2$**
- Increased production
- Increased vasoconstriction
- Increased platelet activation

**Endothelin-1**
- Increased production
- Increased vasoconstriction
- Increased smooth muscle proliferation

**Vasoactive Intestinal Peptide**
- Decreased production
- Decreased platelet inhibition
- Decreased vasodilation

**Serotonin**
- Decreased in platelets
- Increased in serum levels
- Increased vasoconstriction
- Increased smooth muscle hypertrophy and hyperplasia

**Inflammation** (in some cases)
- Increased autoantibodies
- Increased proinflammatory cytokines
- Increased inflammatory infiltrates

**Bone Morphogenic Protein Receptor-2 (BMPR2)**
- Mutations seen in some familial PAH
- Increased vascular cell growth by activating SMAD and LIM kinase

**Hypoxia Inducible Factor-1 alpha (HIF-1 alpha)**
- Increased activation of this transcription factor
- Increased abnormal apoptosis/proliferation ratio

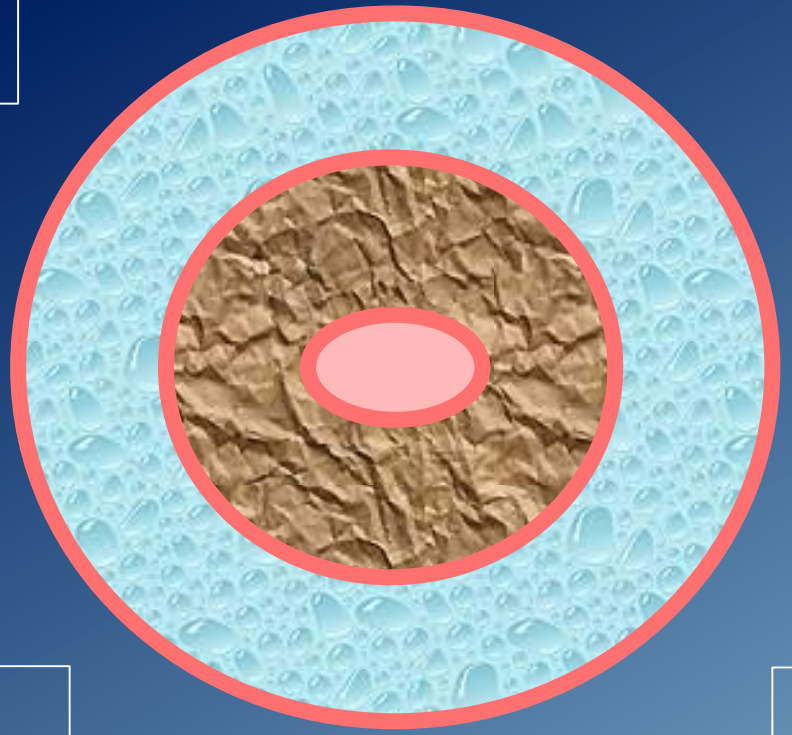
**Augmented Voltage Potassium Channels (Kv1.5)**
- Increased activation of this transcription factor
- Increased abnormal apoptosis/proliferation ratio

**Nuclear Factor Activating T Lymphocytes (NFAT)**
- Increased activation of this transcription factor
- Increased abnormal apoptosis/proliferation ratio

# Pulmonary Artery Hypertension: Pathophysiology[3]

**Molecular Changes**
- Increased endothelial dysfunction
- Decreased apoptosis/proliferation ratio
- Increased activation adventitia metalloproteases

**Plexiform Lesions/Arteriopathy**
- Increased in adventitia
- Disorganized
- Late finding



**Arteriopathy**
- Intimal hyperplasia (late finding)
- Medial hypertrophy (early finding)
- Adventitial proliferation (late finding)

**Thrombus Insitu**
- Endothelial lining

**Inflammation**
- Varying degrees
- ? End result or contributing process

**Right Ventricle**
- Increased hypertrophy
- Increased dilation
- Increased thinning

# Classification of PH

# Classification of PH

- In 1973 WHO organized in Geneva to discuss primary pulmonary hypertension
  - Primary Pulmonary Hypertension (PPH)
    - Diagnosis of exclusion rather than of clinical correlation
  - Secondary Pulmonary Hypertension
    - Diagnosed in conjunction with another confirmed diagnosis

# Classification of PH

- After meeting again in 1998, there was a 5 Group Classification System
  - Categories shared similar symptoms, pathology, and treatment
  - Since then there have been modifications to the Classification System but not to the definitions of each grouping
  - (Iterations: Evian 1998, Venice 2003, Dana Point 2009, Nice 2013, Nice 2018)

# Classification of PH: Group 1: PAH

- PAH is classified as a “syndrome resulting from restricted flow through the pulmonary artery circulation resulting in increased pulmonary vascular resistance and ultimately right heart failure” (ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension).

- Not a disease……**NO CURE!**

# Classification of PH[4]

1. **Pulmonary Arterial Hypertension**

   Idiopathic

   Heritable

   -BMPR2 mutation

   -Other mutations

   Drugs and Toxins

   Associated with:

   -Connective Tissue Disease

   -HIV infection

   -Portal HTN

   -Congenital Heart Disease

   -Schistosomiasis

# Classification of PH: Group 1: PAH Epidemiology

- Incidence is quoted as 6-15pts/1 million[2,3]
  - Left Ventricular Dysfunction more prevalent than PAH
- Scleroderma most common connective tissue disease[5]
- Anorexigen use (higher in France registry than US) [5]
- HIV infection (higher in France registry
- Gender: Women
  - (1.7:1 in NIH registry, 3:1 PHC Registry, 4.8:1 REVEAL Registry, 3.2:1 Mayo Registry)[5]
- Mean age 45-65 years[5]
- Caucasian
  - (72.8%), AA (12.2%), Hispanic (3.3%), Asians or Pacific Islanders (2.8%) (REVEAL Registry)[5]

# Classification of PH[4]

## Group 1: 1’ Pulmonary Veno-Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis

Idiopathic

Heritable

-EIF2AK4 mutation

-Other mutations

Drugs, Toxins and Radiation Induced

Associated with:

-Connective Tissue Disease

-HIV infection

## Group 1: 1” Persistent Pulmonary Hypertension of the Newborn (PPHN)

*ESC/ESR*

# Classification of PH[4]

## Group 1: List of Drugs and Toxins Known to Cause PAH

### Known Risk

- Aminorex *
- Benfluorex *
- Dexfenfluramine*
- Fenfluramine*
- Toxic Rapeseed oil
- Selective SSRI's
  - Newborns

*Off Market in US and most EU

### Probable Risk

- Amphetamines
- Dasatinib (Sprycel)
  - Chemotherapy
- L-tryptophan
- Methamphetamines

### Potential Risk

- Cocaine
- Phenylpropanolamine
- St. John's Wart
- Amphetamine-like Drugs
- Some Chemo agents ie: alkylating agents
  - Mytomicine C
  - Cyclophosphamide
  - Cause pulmonary veno-occlusive disease

ESC/ERS Guidelines 2015

# Classification of PH[4]

## Group 2: Pulmonary Hypertension d/t Left Heart Disease

Left Ventricular Systolic Dysfunction

Left Ventricular Diastolic Dysfunction

Valvular Disease

Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

Congenital/acquired pulmonary veins stenosis *ESC/ESR*

# Classification of PH[4]

## Group 3: Pulmonary Hypertension d/t Lunge Diseases and/or Hypoxia

Chronic Obstructive Pulmonary Disease (COPD)

Interstitial Lung Disease

Other Pulmonary Diseases with Mixed Restrictive and Obstructive Pattern

Sleep-Disorder Breathing

Alveolar Hypoventilation Disorders

Chronic Exposure to High Altitudes

Developmental Lung Diseases *ESC/ESR*

# Classification of PH[4]

**Group 4: Chronic Thromboembolic Pulmonary Hypertension and Other Pulmonary Artery Obstruction**

Chronic Thromboembolic Pulmonary Hypertension

Other Pulmonary Artery Obstructions

Angiosarcoma

Other Intravascular Tumors

Arteritis

Congenital Pulmonary Artery Stenoses

Parasites (hydatidosis)

*ESC/ESR*

# Classification of PH[4]

## Group 5: Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms

Hematological Disorders: Chronic Hemolytic Anemia, Myeloproliferative Disorders, Splenectomy

Systemic Disorders: Sarcoidosis, Pulmonary Histiocytosis, Lymphangioleiomyomatosis, Neurofibromatosis

Metabolic Disorder: Glycogen Storage Disease, Gaucher Disease, Thyroid Disorders

Others: Pulmonary Tumoral Thrombotic Microangiopathy, Fibrosing Mediastinitis, Chronis Renal Failure (with/without dialysis) Segmental Pulmonary Hypertension *ESC/ESR*

# Pulmonary Artery Hypertension: Diagnosis

# Pulmonary Hypertension: Diagnosis

**Subjective Exam**

- Dyspnea
- Fatigue
- Chest Pain
- Syncope or near syncope
- Cough
- Severe cases have exercise induced nausea/vomiting

**Objective Exam**

- Abdominal and/or pedal edema as RV failure progresses
- Hemoptysis
- Hoarseness d/t laryngeal nerve compression
- Left parasternal lift
- Accentuated pulmonary component of S2
- RV 3rd heart sound
- Increased JVP
- Hepatosplenomegaly
- Ascites

# Pulmonary Hypertension: Diagnosis[5]

- Chest X-Ray Findings
  - Central pulmonary arterial prominence
  - Loss of peripheral vascularity
  - Right atrial enlargement
  - Right ventricular enlargement
  - Normal CXR does not exclude PAH
- Electrocardiogram (ECG)
  - Normal ECG does not preclude PAH, abnormal in severe cases
  - P Pulmonale
  - Right axis deviation
  - RV hypertrophy (less sensitive dx)
  - RV strain (more sensitive dx)
  - Right bundle branch block
  - QTc prolongation (may suggest severe PAH)

# Pulmonary Hypertension: Diagnosis[3,5]

- Echocardiography
  - Always performed if suspect PH
  - Not enough to determine treatment course, need RHC
  - RA and RV enlargement
  - Flattening of intraventricular septum
  - eSPAP elevated or peak tricuspid regurgitation velocity (TRV) elevated
  - Tricuspid regurgitation
  - Pericardial effusion present
- Hemodynamic Monitoring
  - Remains gold standard for diagnosing
  - 3 variables noted for increased risk of death
    - Increased mPAP, Increased mRAP, Decreased CI
  - Useful to determine vasodilator responders (vasoreactivity)
  - mPAP > 25 mmHg = PH diagnosis
  - mPAP > 25 mmHg AND PVR > 3 wu = PAH
  - May need to use Fick CO rather than thermodilution CO d/t low CO
  - mVO2: if reduced portends to poor outcomes

# Pulmonary Hypertension: Diagnosis[5]

- Exercise Testing
  - 6 minute walk test
  - Peak $VO_2$
  - Use Borg Scale at end of test
  - Can use exercise right heart catheterizations or echocardiography
    - Good predictor of mortality
    - Very difficult to do
    - Need to be done in centers experienced at performing test
- Functional Class
  - Like NYHA Class I-IV
  - Class I – No limitations
    - Sx: None with ordinary physical activity
  - Class II – Slight limitation
    - Sx: Appear upon ordinary physical activity
  - Class III – Marked limitation
    - Sx: Appear less than ordinary activity
  - Class IV – Severe limitation
    - Sx: Appear upon any physical activity or may be at rest; s/sx RHF

# Pulmonary Hypertension: Diagnosis[3,5]

- CT Scan
  - May reveal PA or RV enlargement
  - Increased PA diameter (≥ 29 mm)
  - Pulmonary:aorta ratio (≥ 1.0)
  - Artery:Bronchus ratio (≥ 1:1 in 3-4 lobes; highly specific for PAH)
  - Rule out CTEPH
  - High resolution CT scan evaluate parenchymal, interstitial or pulmonary vein occlusive disease (PVOD)
  - Pulmonary hemangiomatosis and ground glass appearance + in PAH
- Cardiac MRI
  - Assess RV function and size
  - Prognostic indicators
    - Poor RV function
    - RV SV ≤ 25 ml/$m^2$
    - RVEDD volume ≥ 84 ml/$m^2$
    - LV EDD volume ≤ 40 ml/$m^2$
    - PA stiffness measured as relative cross-sectional area change < 16%

# Pulmonary Hypertension: Diagnosis[3,5]

- Biomarkers
  - BNP elevation
  - NT-proBNP elevation (RV enlargement)
  - Increased uric acid (impaired oxidative metabolism seen in severe functional class)
  - Increased cardiac troponin (RV ischemia)
  - Thyroid function tests (found to be abnormal in PAH)
  - LFT's (RV dysfunction)
  - Hepatitis panel, HIV panel
  - ANA – low titer in PAH 1:80; also connective tissue disorders

# Pulmonary Hypertension: Diagnosis[3,5]

- Other testing:
- Abdominal ultrasound
  - Evaluate portal hypertension
- VQ scan
  - May be helpful in evaluating CTEPH patients
- CPET or CPEX
  - Poor hemodynamic response to exercise good prognosticator of mortality[6,7]

# Pulmonary Hypertension: Treatment

# Pulmonary Hypertension: Treatment – Groups 2-5

- Treat underlying cause(s)
- Inhaled iNO, inhaled epoprostenol, inhaled iloprost can be given short-term post-operatively after cardiac surgery where RVF or PH persists
- Transition to sildenafil if needed
- Oxygen
  - Pulmonary vasculature vasodilator
  - Increases available oxygen to tissues to decrease hypoxemia response, especially in low output states
- CTEPH may require embolectomy
  - Best if performed in centers experienced in this type of procedure
  - May have residual PH requiring aggressive treatment

# Pulmonary Hypertension: Treatment

Courtesy Dr. David Hormuth Collection

# Pulmonary Hypertension: Treatment


Courtesy Dr. David Hormuth Collection

# Pulmonary Artery Hypertension: Treatment – Group 1

- Calcium Channel Blockers
  - Diltiazem, amlodipine, long acting nifedipine
  - Avoid verapamil due to negative inotrope
  - Used only in patients that are vasoreactive or vasoresponsive as proven by RHC with iNO, IV epoprostenol, IV adenosine, or inhaled iloprost
  - Most advantageous in IPAH, HPAH, and drug induced PAH[2,5]
  - Successful vasoreactive test:
    - Decrease mPAP by at least 10 mmHg to an absolute level $\leq$ 40 mmHg without a decrease in cardiac output

# Pulmonary Artery Hypertension: Treatment – Group 1

- Prostanoids
  - Should be administered in centers experienced in giving this class of drugs
    - 1st dose should be administered in the hospital
  - Epoprostenol, iloprost, selexapag, tresprostinil
  - Epoprostenol – closest to intrinsic protanoid; issue is short shelf-life (8 hours in room temperature), short half-life (3-5 mins); use in FC III, IV; being studied in combination therapy
  - Iloprost – IV or Inhalation administration; inhalation requires 6 to 9 doses/day; IV has been shown to be as effective as epoprostenol; oral iloprost has not been studied in PAH; use in FC III, IV

# Pulmonary Artery Hypertension: Treatment – Group 1

- Prostanoids
  - Selexapag, – oral administration; metabolite close to endogenous prostacyclin but chemically different; use in FC II, III, IV
  - Tresprostinil – can be given SQ but very painful; IV associated with increased catheter based infections;  longer half-life (4.5 hours); use in FC II, III, IV
    - Being studied in combination therapy
    - Oral and inhalation compounds in trial

# Pulmonary Artery Hypertension: Treatment – Group 1

- Endothelin Receptor Antagonists (ERA)
  - Should be administered in centers experienced in giving this class of drugs
    - 1st dose should be administered in the hospital
- Ambrisentan, Bosentan, Macitentan
- Ambrisentan – Selective ERA binds with endothelin-1 A; may cause testicular atrophy, teratogenic, birth control methods recommended
- Uses in FC II, III
- Check liver function tests Q month, monthly pregnancy test in women, and periodic HgB tests

# Pulmonary Artery Hypertension: Treatment – Group 1

- Bosentan– Non-selective ERA (binds with endothelin-1 A and B); teratogenic, must use birth control method (barrier better than hormonal as latter may be less effective)
- Use in FC III, IV
- Check liver tests Q month, HCT Q 3 months

- Macitentan – Non-selective ERA like bosentan; teratogenic, must use birth control method
- Use in FC II, III
- No liver implications but HgB is known to decrease

# Pulmonary Artery Hypertension: Treatment – Group 1

- Phosphodiesterase Inhibitors (PDE-5 Inhibitors)
- Increase iNO activates cGMP causing increased vasodilation
- Oral agents
- Interactions with CYP3A, CYP450 medications
- Sildenafil, Tadalafil, Riociguat (cGMP pathway), Vardenafil
- Sildenafil – short acting, usually requires TID dosing
- Vardenafil – longer acting, BID dosing
- Tadalafil – longer acting, daily dosing
- Riociguat – induces cGMP production where as the others enhance NO-cGMP; TID dosing

# Pulmonary Artery Hypertension: Treatment – Group 1 Combination Therapy[4]

- Not in current US guidelines
- Under investigation
  - BREATHE-2 (epoprostenol/bosentan)
  - AMBITION (ambrisentan/tadalafil)
- Most medication regimens are sequential, adding medications to current therapy not starting on combination therapy initially

| Measure/ treatment | Class[a]-Level[b] | | | | | | Ref.[c] |
|---|---|---|---|---|---|---|---|
| | WHO-FC II | | WHO-FC III | | WHO-FC IV | | |
| Ambrisentan + tadalafil[d] | I | B | I | B | IIb | C | 247 |
| Other ERA + PDE-5i | IIa | C | IIa | C | IIb | C | - |
| Bosentan + sildenafil + i.v. epoprostenol | - | - | IIa | C | IIa | C | 246 |
| Bosentan + i.v. epoprostenol | - | - | IIa | C | IIa | C | 198, 245 |
| Other ERA or PDE-5i + s.c. treprostinil | | | IIb | C | IIb | C | - |
| Other ERA or PDE-5i + other i.v. prostacyclin analogues | | | IIb | C | IIb | C | - |

ESC/ERS Guidelines 2015

# Pulmonary Hypertension: Surgical Treatment

- Thromboendarterectomy
  - May still have PH post-operatively/chronically
- Atrial Septostomy
  - Create a right-left atrial shunt to decrease right sided filling pressures
  - De-oxygenated blood into circulatory system but improved CO possibly outweighs the decrease (more blood supply vs. O2 content)
- Combined Heart-Lung Transplant
  - Early referral better outcome
  - Survival for PAH patients less than survival for all other reasons for transplant

# Pulmonary Hypertension:

Questions???

# Many Thanks To:

# Pulmonary Hypertension: References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