International Society for Heart and Lung Transplantation
(ISHLT)

# Pulmonary Hypertension
# Core Competency Curriculum
# (ISHLT PH CCC)

SECOND EDITION (2018)

The Educational Leadership of the
ISHLT Pulmonary Hypertension Council

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Pulmonary Hypertension Council Leadership

## ISHLT Pulmonary Hypertension CCC:
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# Introduction

# I. Introduction to Pulmonary Hypertension

Learning Objectives for the Introduction to Pulmonary Hypertension

1) To establish context and historic background for pulmonary hypertension.
2) To know how to define and classify pulmonary hypertension
3) To understand that pulmonary hypertension is an increasingly recognized condition of many causes that is uniformly associated with reduced survival
4) To learn the FDA approved indications for all of the currently available specific therapies for pulmonary arterial hypertension
5) To understand the risks of misclassification of PH and misuse of approved specific therapies for pulmonary arterial hypertension
6) Understand what physicians are treating PH patients
7) Recognize the need for training and core competencies in pulmonary hypertension

1. **Background**
    a. **Historical Context**
    b. **Evolution of clinical classification of Pulmonary Hypertension**
        i. **Historical WHO Classification Systems Overview**
2. **Definition and Classification of Pulmonary Hypertension**
    a. **Definition of Pulmonary Hypertension**
    b. **Hemodynamic classification**
        i. **Pre-capillary PH**
        ii. **Post-capillary PH**
        iii. **Isolated post capillary PH, Combined post- and precapillary PH and the role of hemodynamic markers**
    c. **Clinical Classification**
        i. **Current Nice Classification**
3. **Impact of Pulmonary Hypertension on Multiple Disease States: Overview and Examples**
    a. **PH reduces survival across multiple diseases**
        i. **Left heart failure**
            1. **HFpEF and HFrEF survival with/without PH**
        ii. **Risk of heart transplantation with PH**
        iii. **Impact on survival with PH in COPD and IPF**
        iv. **Scleroderma survival**
            1. **Survival in scleroderma with PAH, ILD, neither, and both**
            2. **ILD survival with/without PH**
        v. **Portal hypertension and liver transplantation**
            1. **Poor survival PoPH (French, REVEAL, UK PAH registry)**
            2. **Risk of liver transplant with PH**
        vi. **Idiopathic pulmonary arterial hypertension**
            1. **NIH survival curve**
            2. **Contemporary survival curves in international registries**
    b. **Right Ventricular Failure**

- i. **The Final Common Pathway That Determines Prognosis in Pulmonary Hypertension**
- ii. **Pathophysiology of RV failure in PH**
  1. **Adaptive and maladaptive RVH**
  2. **RV enlargement**
  3. **RV failure**
  4. **RV-PA coupling**
- iii. **Assessment of the RV function**
  1. **Imaging**
     a. **Echo**
     b. **MRI**
     c. **CT**
     d. **Experimental modalities such as CT-PET**
  2. **Invasive hemodynamics**
  3. **CPET**
- iv. **Management of RV function and failure in PH**
  1. **Preload reduction- diuretics**
  2. **Afterload reduction- pulmonary vasodilator therapies**
  3. **Contractility (role of inotropic support, negative impact of systemic vasodilators)**
  4. **Other medical and interventional (ECMO) therapies**

4. **<u>Physician Specialties Currently Treating PH</u>**
   a. **Pulmonologists**
   b. **Cardiologists**
   c. **Anesthesiologists**
   d. **Cardiac and Thoracic surgeons (Transplantation, conventional surgery)**
   e. **Primary Care Providers**
   f. **Rheumatologists**
5. **<u>Recognition of the Need for PH Training and Core Competencies</u>**
   a. **Complexity of Diseases and Diagnostic Evaluation**
   b. **Risks of inadequate monitoring and follow-up**
      i. **Young patients with PAH left undertreated until advanced, irreversible disease with severe right heart failure and very poor prognosis evident**
      ii. **Frequency of death with PAH on oral therapy**
   c. **Risks of misclassification of PH**
      i. **Pulmonary hypertension due to HFpEF misclassified as PAH and treatment with PH therapies that may worsen HF and symptoms**
      ii. **Group 3 PH misclassified as PAH and treated with therapies that may worsen V/Q mismatch and hypoxemia**
      iii. **PAH misclassified as PH due to HFpEF**
         1. **Disease with very poor survival and therapeutic options left untreated**
      iv. **CTEPH undiagnosed or misdiagnosed as PAH**
         1. **Treatable/curable condition left untreated**
   d. **Introduction to Currently Available PH specific drugs, FDA indications, and potential risks of use with non-PAH PH**
      i. **Endothelin receptor antagonists**

1. **Ambrisentan, bosentan and macitentan**
2. **Globally approved indications**
3. **Potential/theoretical risks in non-PAH PH**
   a. **Fluid retention and worsened HF in Group 2 PH**
   b. **Worsened V/Q mismatching and hypoxemia in Group 3 and 4 PH**

**ii. Prostacyclin analogues**

1. **Epoprostenol, treprostinil, iloprost**
2. **Oral IP3 agonists e.g. selexipag**
3. **Globally approved indications**
4. **Potential/theoretical risks in non-PAH PH**
   a. **Worsened HF outcomes in Group 2 PH**
   b. **Worsened V/Q mismatching and hypoxemia in Group 3 PH (intravenous/systemic administration)**

**iii. soluble Guanylate cyclase activators/stimulators**

1. **Riociguat**
2. **Globally approved indications**
3. **Elevated risk in non PAH, non CTEPH PH**

**iv. Phosphodiesterase type 5 inhibitors**

1. **Sildenafil and tadalafil**
2. **Globally approved indications**
3. **Potential/theoretical risks in non-PAH PH**
   a. **Hypotension**
   b. **V/Q mismatch and hypoxia (systemic administration, more theoretical)**
   c. **Unknown effect in most indications, contra indication in PH post valvular interventions**

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# II. Evaluation of Pulmonary Hypertension

Learning objectives for the evaluation of Pulmonary Hypertension

1) To know common presenting symptoms and scenarios in PH
2) To know risk factors for pulmonary hypertension
3) To know common physical findings in pulmonary hypertension and distinguishing features of pulmonary arterial and post capillary pulmonary hypertension
4) To understand the required diagnostics to properly classify PH in order to treat based on guidelines
5) To understand the diagnostic utility and limitations of echocardiography for PH, including required measures, and assessment of the right ventricle and ventricular interdependence
6) To know how to perform and interpret a diagnostic right heart catheterization for suspected PH, the importance of vasodilatory testing, common mistakes and pitfalls with hemodynamic measures
7) To understand when it is appropriate to measure a left heart catheterization to measure LVEDP
8) To know why and how to perform exercise testing in PH, and its prognostic value
9) To learn the prognostic value of exercise measures in PH
10) To discuss laboratory testing, imaging, and hemodynamic biomarkers in PH
11) To understand the risk, benefits, and ethics of screening high risk populations

## 1. History and Physical Examination

- **a. Common presenting symptoms of PH and right heart failure**
  - **i. Dyspnea**
  - **ii. Fatigue**
  - **iii. Chest pain**
  - **iv. Exertional Dizziness/Pre-syncope/Syncope**
  - **v. Increased abdominal girth**
  - **vi. Leg swelling**
  - **vii. Early versus late symptoms**
- **b. Signs of PH and right heart failure on exam**
  - **i. Elevated JVP**
  - **ii. Left parasternal lift**
  - **iii. Accentuated P2 component of S2**
  - **iv. Murmur of tricuspid regurgitation**
  - **v. Right ventricular gallop**
  - **vi. Hepatomegaly, pulsatile liver**
  - **vii. Ascites**
  - **viii. Edema**
  - **ix. Early versus late disease findings**
  - **x. Physical clues to secondary causes of PH**
- **c. Symptoms and signs suggestive of left heart failure**
  - **i. Orthopnea, PND**
  - **ii. Pulmonary rales**
  - **iii. Sleep apnea**
  - **iv. History of atrial fibrillation**

- **d. Risk factors for PAH and associated conditions leading to PAH**
  - **i. Drugs and toxins**
  - **ii. Connective tissue disease**
  - **iii. Family history of PAH**
  - **iv. HIV infection**
  - **v. Portal Hypertension**
  - **vi. Chronic hemolytic anemias**
- **e. Risk factors for PH from other conditions**
  - **i. Chronic, advanced left heart failure**
  - **ii. Advanced lung disease**
  - **iii. History of PE**
  - **iv. Sarcoidosis**
  - **v. Splenectomy**
  - **vi. Myeloproliferative disorders**

**2. <u>Common Presenting Scenarios in PH</u>**

- **a. Obese patient with CRFs presenting with DOE**
- **b. Young woman with DOE not responding to inhalers for asthma**
- **c. Middle aged man presenting with DOE and CP admits to meth use**
- **d. Older woman with scleroderma c/o worsening DOE and exertional dizziness**
- **e. Middle aged male with former heavy EtOH use and/or HCV c/o SOB and worsened abdominal distention**

**3. <u>Diagnostic Testing</u>**

- **a. Echocardiography**
  - **i. Utility and limitations**
  - **ii. Required measures**
  - **iii. TR jet velocity and accuracy of PASP estimate**
  - **iv. Shunt study**
  - **v. Ventricular interdependence**
  - **vi. RV/PA coupling**
- **b. Laboratory testing**
  - **i. ANA**
  - **ii. HIV**
  - **iii. Hepatitis serologies**
  - **iv. LFTs**
  - **v. TFTs**
- **c. Pulmonary function testing**
  - **i. DLCO, FVC/DLCO ratio**
  - **ii. ABGs**
  - **iii. HRCT chest**
- **d. Radiological Investigations**
  - **i. High Resolution CT**
  - **ii. CT pulmonary angiogram**
  - **iii. Ventilation-Perfusion scintigraphy and role of SPECT**
  - **iv. Invasive pulmonary angiography**
  - **v. Cardiac MRI and MR pulmonary angiography**
- **e. Right heart catheterization**
  - **i. Pulmonary artery catheter and how to perform catheterization**

   - **ii. Required hemodynamic measures**
   - **iii. Oxygen saturation shunt run**
   - **iv. Acute Vasodilator testing in PAH**
   - **v. Role of Exercise and fluid challenge at RHC to uncover PH HFpEF**
   - **vi. Common mistakes and pitfalls**
   - **vii. When to perform left heart catheterization to measure LVEDP**
   - **viii. Common hemodynamic scenarios**
- **f. Exercise testing**
   - **i. When to consider exercise testing in PH**
   - **ii. Exercise modalities in PH**
      1. **RHC**
      2. **CPET**
      3. **6 MWT**
   - **iii. Exercise testing for routine clinical evaluation and research in PH**
- **g. Biomarkers in Pulmonary Hypertension**
   - **i. NT-proBNP, uric acid, eGFR, serum Cr, troponin**
   - **ii. CRP, angiopoeitins**
- **h. Risks and benefits of screening of high risk populations for PAH**
   - **i. Echo**
   - **ii. Exercise echo**
   - **iii. MRI**
   - **iv. Genetics testing**
   - **v. Ethics of screening**

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## III. Pulmonary Arterial Hypertension (WHO Group 1 PH)

Learning Objectives for Pulmonary arterial hypertension

1) To understand the pathophysiology of PAH
2) To learn the epidemiology of PAH
3) To understand the genetics of PAH
4) To discuss prognosis in PH based on etiology
5) To learn baseline and follow up prognostic markers of PAH
6) To understand and apply the concept of risk stratification
7) To understand the classes of drugs approved to treat PAH, common side effects, and the use of combination therapy
8) To understand guideline recommendations for follow-up care and objective measures reassessment in PAH
9) Know the indications, timing, challenges, and outcomes of PAH patients referred for lung transplantation, including the LAS score and modification for PAH
10) To discuss the use of mechanical support devices (ECMO, Nova-Lung) as a bridge to lung transplant in PAH based on clinical experience and case cohort studies, economic considerations, and devices under development
11) To recognize end-stage PAH disease, understand common end-of-life issues including the risks of endotracheal intubation, utility of ACLS with cardiac arrest, in PAH
12) Understand the role of palliative care and learn the steps in forming a palliative care team for PAH patients
13) Learn how to utilize the ISHLT registry report and resources

1. **<u>Pathophysiology of Pulmonary Arterial Hypertension</u>**
   a. **Pulmonary Arterial Pathology**
      i. **Pulmonary artery vasoconstriction**
      ii. **Endothelial dysfunction**
      iii. **Pulmonary artery smooth muscle cell hypertrophy and hyperplasia**
      iv. **Pulmonary artery adventitial changes**
      v. **Plexogenic lesions**
      vi. **In situ thrombosis**
      vii. **Inflammation**
   b. **Right ventricular dilatation and failure**
   c. **Ventricular interdependence**
2. **<u>Epidemiology of Pulmonary Arterial Hypertension</u>**
   a. **Idiopathic**
   b. **Genetics in PAH**
      i. **Familial/Heritable PAH**
      ii. ***BMPR2*, ALK, endoglin (w/ or w/o HHT), unknown genes**

- **c. Drug and toxin induced**
  - **i. Definite, very likely, possible, or unlikely risk factors**
- **d. Associated PAH**
  - **i. Connective tissue disease**
    - **1. Scleroderma (limited and diffuse), SLE, others**
  - **ii. HIV**
  - **iii. Portal hypertension**
  - **iv. Congenital heart disease**
  - **v. Schistosomiasis**
  - **vi. Chronic hemolytic anemias**
- **e. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**

**3. <u>Survival in Pulmonary Arterial Hypertension</u>**

- **a. Impact of etiology on survival**
- **b. Lessons from registries (US and non US)**

**4. <u>Prognostic Factors in PAH</u>**

- **a. Functional Class**
  - **i. WHO and NYHA Functional Classification System**
  - **ii. Survival based on Functional Class**
    - **1. Baseline**
    - **2. Follow-up**
- **b. Exercise capacity**
  - **i. 6 minute walk test**
    - **1. Baseline**
    - **2. Follow-up**
  - **ii. Cardiopulmonary exercise test**
  - **iii. Other: treadmill, shuttle test**
- **c. Biomarkers**
  - **i. BNP**
  - **ii. Others**
- **d. Hemodynamics**
  - **i. RA pressure, CO/CI, PAP, PVR**
  - **ii. Others**
- **e. Echocardiography**
- **f. MRI**
- **g. PFTs –DLCO**
- **h. Hospitalisations**

**5. <u>Risk Stratification in PAH</u>**

- **a. <u>Principles of integrated approach</u>**
- **b. <u>Tools available</u>**
- **c. <u>Evidence from recent analysis and importance in management</u>**

**6. <u>Treatment of PAH</u>**

- **a. <u>Non specific, background Therapies and Calcium Channel Blockers</u>**
- **b. <u>Specific PAH therapies</u>**
  - **i. <u>Classes of drugs</u>**
  - **ii. <u>Side effect profile</u>**
- **c. <u>Guideline based treatment algorithm</u>**

   d. **Combination Therapy**
      i. **Upfront dual combination**
      ii. **Sequential combination**
      iii. **Triple therapy**
      iv. **Consideration of transition of agents**
      v. **On going Clinical Trials e.g. role of triple therapy**
7. **<u>Lung Transplantation</u>**
   a. **Indications in PAH**
   b. **Timing of Referral for PAH**
   c. **Survival after Lung Transplantation for PAH**
8. **<u>End-stage PAH disease</u>**
   a. **Recognize treatment failure**
      i. **Right heart failure**
   b. **End-of-Life Issues**
      i. **Advanced Directives**
      ii. **Risks of Endotracheal Intubation with PAH**
      iii. **ACLS Effectiveness After Cardiopulmonary Arrest with PAH**
   c. **Palliative Care**
      i. **Role of Palliative Care**
      ii. **Steps in Forming a Palliative Care Team**
9. **<u>How to Utilize the ISHLT Registry Report and Resources</u>**

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## IV. Pulmonary Hypertension due to Left Heart Failure (Group 2 PH)

Learning Objectives for Pulmonary Hypertension due to Left Heart Failure

1) To review the epidemiology of Group 2 PH and the prognosis of PH in left heart disease
2) To understand when to consider PH is related to LHD
3) To learn the pathophysiology of pulmonary hypertension in left heart disease, including pulmonary vascular remodeling and PH out of proportion
4) Learn the diagnostic evaluation of patients with suspected Group 2 PH
5) To review the hemodynamics and understand the fundamental differences between Group 1 and Group 2 PH
6) To review therapeutic options based on clinical trial data in Group 2 PH
7) To learn the risks and management of PH in heart transplant candidates
8) Learn strategies to manage PH and right heart failure in patients undergoing LVAD implantation

1. **<u>Overview of Pulmonary hypertension due to left heart failure</u>**
   a. **HFpEF and HFrEF**
   b. **valvular left heart disease**
2. **<u>Epidemiology and Prognostic Significance of PH in Left Heart Disease</u>**

a. **HFrEF and PH**
b. **HFpEF and PH**
c. **PH with aortic and mitral valve disease**

3. **<u>Pathophysiology of PH in Left Heart Disease</u>**
   a. **Passive pressure elevation**
   b. **Pulmonary Vasoconstriction**
   c. **Pulmonary vascular remodeling**
4. **<u>Hemodynamic Definitions and Classification of PH due to Left Heart Disease</u>**
   a. **Review hemodynamic definitions, terms, and fundamental differences from PAH**
      i. **Key Hemodynamic Variables**
         1. **PCWP/LVEDP, TPG, PVR calculation**
      ii. **Post-capillary/Passive/Pulmonary Venous Hypertension from LHD**
      iii. **Combined post- and precapillary PH**
         1. **Fixed/Non-reactive**
      iv. **Pre-capillary PH from Group I, Group 3, Group 4, and often Group 5 PH**
      v. **Borderline PCWP/LVEDP zone between pre- and post-capillary PH**

5. **<u>Diagnosis of Group 2 PH</u>**

   a. **History and Physical Clues**
      i. **Age > 65 y/o**
      ii. **HTN**
      iii. **Obesity, metabolic syndrome**
      iv. **Coronary heart disease**
      v. **Diabetes Mellitus**
      vi. **Atrial fibrillation**

   b. **Echo evaluation**
      i. **LV ejection fraction, wall thickness and motion**
      ii. **LV diastolic function by Doppler and TDI**
      iii. **LA size, morphology**
      iv. **Right heart evaluation**
      v. **Diagnostic challenges**
         1. **LV diastolic function in atrial fibrillation**
         2. **Pitfalls of LV diastolic function analysis**
   c. **Biomarkers**
      i. **BNP, NTpro-BNP and levels in relation to PAH**
   d. **MRI**
   e. **Evaluation for CAD**
      i. **Indications**
      ii. **Non-invasive stress testing**
         1. **Consider timing before catheterization**
      iii. **Coronary angiography**
   f. **Pre (non invasive) test to predict PH due to left heart disease**

**g. Invasive confirmation of PH in left heart disease**

**i. Indications**
**Symptoms not responding to treatment of LHD**
**PH with preserved EF unless mod-severe diastolic dysfunction by echoP**
**PH with afib and normal EF**

**ii. Provocative testing during catheterization**
1. **Fluid challenge**
2. **Exercise**
3. **Vasodilator testing (Nitroprusside vasoreactivity testing in heart transplant/VAD candidates)**

**iii. Left heart catheterization**
1. **LVEDP direct measuremen**
2. **Routine to confirm elevated PCWP**
3. **Unable to wedge PA catheter**
4. **Blood gas from wedged PA catheter not fully saturated**

**i. Simultaneous LHC/RHC hemodynamics e.g. pericardial disease**
**ii. Coronary angiography**

**6. <u>Treatment of PH Related to Left Heart Disease</u>**
- **a. Diuretics**
- **b. Evidence-based therapy for HFrEF**
- **c. Lack of effective pharmacotherapy for HFpEF**
- **d. Surgery as indicated for valve or pericardial disease**
- **e. Vasodilator Therapies**
  - **i. Nitrates**
  - **ii. PAH specific therapies in LHD**
    1. **Clinical Trial Evidence of Prostanoids, ERAs, and PDE5I in heart failure**
    2. **Risks/concerns for use in LHD e.g. precipitation of pulmonary oedema with ERA, clinical worsening in PH due to valvular heart disease**
    3. **Future/ongoing trials of LHD**

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## V. Pulmonary Hypertension in Lung Disease and/or Hypoxia (WHO Group 3 PH)

Learning Objectives for Pulmonary Hypertension due Pulmonary Disease

1) To understand the fundamental differences between Group 1 and Group 3 PH
2) To review the epidemiology of Group 2 PH and the prognosis of this group
3) Pathophysiology
4) Diagnosis
5) To review therapeutic options based on clinical trial data in Group 3 PH
6) To discuss the challenges of mixed PH classification patients

1. **Overview of PH in Lung Disease and/or Hypoxemia**
   a. **COPD**
   b. **ILD (IIP, ILD from CTD, HP, etc)**
   c. **Sleep apnea**
      i. **Obstructive**
      ii. **Central**
   d. **Obesity hypoventilation disorders**
   e. **High Altitude**
   f. **Developmental Abnormalities**
2. **<u>Epidemiology and Prognostic Significance of PH in Lung Disease and/or Hypoxemia</u>**
   a. **PH with COPD**
   b. **PH with IPF**

- **c. PH with ILD in CTD**
- **d. PH and OSA**
  - **i. Association with Group 2 PH**
  - **ii. Prevalence in Group 1 PH (PAH)**
- **e. High Altitude PH**

**3. <u>Pathophysiology of PH in Group 3 PH</u>**

- **a. Hypoxic Pulmonary Vasoconstriction**
- **b. Destruction of Pulmonary Capillary Surface Area**
  - **i. COPD/emphysema**
  - **ii. Alpha-1 antitrypsin deficiency**
  - **iii. Pulmonary Langerhans Histiocytosis X**
- **c. Vasoreactive and Profibrotic Mediators in ILD**
  - **i. IPF**
  - **ii. ILD in CTD**
- **d. Mediators in common with PAH**

**4. <u>Diagnostic Evaluation of PH Related to Lung Disease and/or Hypoxemia</u>**

- **a. ABGs**
- **b. Pulmonary Function Testing**
  - **i. DLCO**
  - **ii. FVC, FEV1, FEV1/FVC ratio, bronchodilator reversibility**
  - **iii. FVC/DLCO ratio in ILD and PH**
- **c. Computed Tomography**
  - **i. HRCT Chest without Contrast**
    1. **Evaluate for ILD**
  - **ii. Volumetric CT**

**5. <u>Treatment of PH Related to Lung Disease and/or Hypoxemia</u>**

- **a. Oxygen supplementation**
- **b. Bronchodilator Therapy**
- **c. Immunosuppression**
- **d. PAH Specific Therapies**
  - **i. Clinical Trial Evidence**
    1. **BUILD 1&3 in IPF**
    2. **Bosentan in COPD**
    3. **COPD arm in ARIES 3**
    4. **Ventavis in COPD**
    5. **ACTIVE Trial of iloprost in IPF**
    6. **ARTEMIS-IPF and ARTEMIS-PH Trials**
    7. **STEP-IPF Trial**
    8. **BUILD 2 in SSc ILD**
    9. **RISE-IIP**
    10. **BPhIT study**
    11. **Others?**
  - **ii. Potential Risks of pulmonary vasodilator therapies with Group 2 PH**
    1. **Worsened V/Q mismatch and hypoxemia with Systemic Administration**
    2. **Exception: Oral PDE5I sildenafil may paradoxically improve V/Q matching and oxygenation in IPF/ILD**

   a. **Modulation of HPV by oral PDE5I sildenafil**

6. **<u>Challenges in Mixed PH Etiologies</u>**
   a. **Scleroderma lung disease**
      i. **Is it Group 1 or Group 3 PH?**
      ii. **FVC/DLCO ratio**
      iii. **<u>Management considerations</u>**
   b. **PH "out of proportion" to lung disease**

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[37-44]


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# VI. Chronic Thromboembolic Pulmonary Hypertension (WHO Group 4 PH)

Learning Objectives for Pulmonary Hypertension due Chronic Thromboembolic Pulmonary Hypertension

1) To review the epidemiology of Group 4 PH and the prognosis of this group
2) To learn the pathophysiology of PH in CTEPH

3) To review the diagnostic evaluation of PH related to chronic pulmonary thromboemboli
4) To learn the therapeutic options for CTEPH based on clinical trial data

Most of this topic will be covered by the CTEPH council so is not comprehensively covered here.

1. **<u>Epidemiology of CTEPH</u>**
   a. **Incidence/prevalence (proximal operable disease vs distal disease)**
   b. **Survival**
   c. **Registry data from Europe (International CTEPH registry)**
2. **<u>Pathophysiology of PH in Group 4 PH</u>**
   a. **Macrovascular obstruction**
   b. **Hypoxic Pulmonary Vasoconstriction**
   c. **Small vessel arteriopathy**
      i. **Medial hypertrophy**
      ii. **Intimal proliferation**
      iii. **Plexiform lesions**
      iv. **Microvascular thrombosis**
      v. **Mediators**
3. **<u>Diagnostic Evaluation of PH Related to CTEPH</u>**
   a. **Ventilation/Perfusion Scan**
   b. **Volumetric Computed Tomography**
      i. **High resolution aspect will r/o ILD**
   c. **Pulmonary angiography**
   d. **Other: PVR calculations done at UCSD, evaluation of microcirculatory reserve**
4. **<u>Treatment of CTEPH</u>**
   a. **Referral to center of excellence**
   b. **Oxygen Supplementation**
   c. **Pulmonary Thromboendarterectomy Surgery**
      i. **Indications/contraindications**
      ii. **Outcomes**
   d. **PAH Specific Therapies**
      i. **Licensed therapy**
         1. **Riociguat**
      ii. **Clinical Trial Evidence**
         1. **Riociguat and PATENT Trial**
         2. **Macitentan and Merit trial**
      iii. **Recurrent/persistent PH after PTE surgery**
      iv. **Non-surgical candidates**
      v. **Use as "bridge to surgery"**
   e. **Balloon Pulmonary-Artery Angioplasty**
      i. **Patient selection**

Selected References and Resources
[45]

1. Kim, N.H., et al., *Chronic thromboembolic pulmonary hypertension.* Journal of the American College of Cardiology, 2013. **62**(25 Suppl): p. D92-9.

## VII. Pulmonary Hypertension with Multifactorial or Unclear Mechanisms (WHO Group 5 PH)

Learning Objectives for Pulmonary Hypertension due Miscellaneous Causes

1) To understand the fundamental differences between Group 1 and Group 5 PH
2) To review the epidemiology of Group 2 PH and the prognosis of this group
3) To review therapeutic options in Group 5 PH

**(This may change based on NICE meeting)**

1. **<u>Review of PH with unclear/multifactorial mechanisms</u>**
   - **a. Hematologic (myeloproliferative d/o, splenectomy)**
   - **b. Systemic d/o (sarcoidosis, pulmonary Langerhans histiocytosis, neurofibromatosis, vasculitis)**
     - **i. Sarcoidosis- presentation can be Group 3 (pulmonary fibrosis), Group 2 (sarcoid heart disease), Group 1 and1' (PVOD by pulmonary vein and pulmonary artery granulomas), extrinsic PA compression by adenopathy, or mixed mechanisms**
   - **c. Metabolic (glycogen storage diseases, Gaucher disease, thyroid disease)**
   - **d. Other (tumor microemboli, fibrosing mediastinitis, PA compression by adenopathy or extrinsic tumor, chronic hemodialysis)**
2. **<u>Diagnostic Evaluation of PH Related to unclear/ multifactorial mechanisms</u>**
   - **a. R/O Group I-IV**
   - **b. Clues based on History, CBC, TFTs, CXR, other chest imaging**
3. **<u>Treatment of Group 5 PH</u>**
   - **a. Hematologic**
     - **i. Similar to Group 1**
     - **ii. Evidence**
   - **b. Systemic**
     - **i. Similar to Group 1 but r/o PH Group 2 and overwhelming Group 3**
   - **c. Metabolic**
     - **i. Treat underlying disease**
     - **ii. PAH therapies ?**
   - **d. Extrinsic PA compression: treat underlying causative disease or mechanical obstruction**

Selected References and Resources
[2, 46-49]

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## VIII. Clinical Research in PAH

Learning Objectives for Clinical research in PAH

1) To review currently enrolling clinical trials in PAH
2) To discuss potential new targets for therapeutics
3) To discuss novel trial design
4) To discuss the ethics in clinical trials for an orphan disease

1. **Currently enrolling and planned Clinical Trials in PAH**
   a. **Phase 2 trials**
      i. **Ralinepag**
      ii. **Inhaled NO**
      iii. **Zamicastat**
   b. **Rituximab in SSC-PAH**
   c. **Triton and triple upfront therapy**
   d. **Replace and Riociguat**
   e. **FREEDOM-Ev**
   f. **Others**
2. **Recently Completed Clinical Trials**
   a. **Riociguat in ILD-PH (RISE-IIP)**
   b. **PORTICO study**
   c. **Griphon**

3. **Potential New Targets for Therapeutics**
4. **Novel Trial Design**
5. **Ethics in Clinical Trials for an Orphan Disease**
6. **Currently Enrolling Clinical Trials in Secondary PH**
   a. **iNO study in Group 3 PH**
   b. **Riociguat in ILD-PH**
   c. **Riociguat in CTEPH-LTE**

Selected References and Resources
[50-55]

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2. Gomberg-Maitland, M., *Traditional and alternative designs for pulmonary arterial hypertension trials.* Proceedings of the American Thoracic Society, 2008. **5**(5): p. 610-6.
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## IX. Treatment of Acute Decompensated Right Heart Failure in PH

Learning Objectives for Acute Decompensated Right Heart Failure in PH

1) Understand the precipitating factors for acute decompensating right heart failure in PH
2) Learn how to manage acute decompensated right heart failure with PH
3) Understand how to transition from acute to chronic therapies for PH and RV failure
4) Learn how to "bridge" PAH patients to lung transplantation with mechanical devices

1. **<u>Identify and treat underlying precipitating factors</u>**
   a. **Dietary indiscretion, infection, anemia/erythrocytosis, dysrhythmia, thyroid disorder, pulmonary embolus**
2. **<u>Restore oxygenation</u>**
   a. **Goal O2 sat 100%, avoid acidemia and hypercarbia**
   b. **High flow O2 if needed**
   c. **Mechanical ventilation high risk, consider risk vs benefit**
   d. **Consider ELCS/ECMO if needed**
3. **<u>Restore vital organ perfusion</u>**
   a. **Pulmonary vasodilators**
      i. **Inhaled NO/epoprostenol/Other inhaled vasodilators**
      ii. **IV epoprostenol (candidates for chronic IV epo therapy)**
      iii. **IV sildenafil**
      iv. **Combination therapy**
   b. **Inotropes and vasopressors**
      i. **Inotropes (IV dobutamine, dopamine)**
      ii. **Inodilators (IV milrinone)**
      iii. **Vasopressors (IV vasopressin, phenylephrine)**
      iv. **Inopressors (IV norepinephrine, epinephrine)**
4. **<u>Treat volume overload</u>**
   a. **IV bolus + IV infusion loop diuretic**
   b. **IV or oral thiazide diuretic**
   c. **Oral aldosterone antagonist**
   d. **Addition of B-adrenergic inotropic agent**
   e. **Mechanical fluid removal (haemofiltration)**
5. **<u>Stabilization Achieved</u>**
   a. **Wean NO with IV epoprostenol or treprostinil (or consider subcutaneous)**
   b. **Wean IV inotropic agents**
   c. **Optimize chronic therapies**
6. **<u>Refractory/Unstable cases (Bridge to Lung Transplantation for Candidates)</u>**
   a. **IV epoprostenol + other pulmonary vasodilators**

   b. **Inotropic support (B-adrenergic agonists, digoxin, diuretic therapy)**
   c. **ECLS (V-A ECMO/ECLS/RVAD)**
   d. **Percutaneous atrial septostomy**
7. **<u>Unstable and/or refractory cases (NOT a candidate for Lung Transplantation)</u>**
   a. **Palliation of symptoms**
      i. **Oxygen**
      ii. **Diuretics**
      iii. **Inotropes home infusion**
      iv. **Liberal use of narcotics**
      v. **Atrial septostomy**
      vi. **Discussion on do not resucitate**
   b. **Hospice**

Selected References and Resources
[5, 56-60]


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## X. Surgery and Anesthesia in Pulmonary Hypertension

Learning Objectives

1) To learn the outcomes of patients with PAH and PH undergoing anesthesia and surgery
2) To learn the physiologic effects and risks of anesthesia and mechanical ventilation in patients with PH
3) To discuss the peri-operative considerations, including screening of at-risk populations, and management of patients with PH
4) To learn intra-operative and post-operative management strategies for patients with PH
5) To understand special surgical considerations (obstetrics, orthopedic, laparoscopic, thoracic/lobectomy)

1. **Outcomes of Patients with PH who Undergo Anesthesia and Surgery**
    a. **Peripartum Eisenmenger patients**
        i. **Historic and contemporary reports**
    b. **Cardiac surgery with PH**
    c. **Noncardiac surgery with PH**
2. **Effects of Anesthesia on the Pulmonary Vasculature**
    a. **Anesthetics agents**
        i. **Vasodilation, myocardial depression and effects in PH**
            1. **Systemic hypotension**
            2. **Decreased coronary perfusion pressure**
            3. **RV ischemia**
            4. **Reduced RV stroke volume**
            5. **Reduced LV preload and stroke volume**
        ii. **Differences in physiologic effects on pulmonary vascular vs systemic vascular resistance of various agents**
            1. **SVR vs PVR of various anesthetic agents**
            2. **Myocardial effects of anesthetic agents**
        iii. **Inaccuracies in assumptions of physiologic effects and guiding principles**
            1. **Variable physiologic effects in the literature**
            2. **All anesthetics can reduce systemic pressure and precipitate decompensation in PH and RV failure**
        iv. **Preferred anesthetic agents/combos in patients with PH**
3. **Effects of Mechanical ventilation on PVR and RV function**
    a. **Induction with anesthesia**
        i. **Systemic vasodilation and hypotension**
        ii. **Increased RV afterload**
    b. **Pulmonary vascular resistance**
        i. **Tidal volume**
        ii. **PEEP**
        iii. **FiO2**
    c. **Worsened hypoxemia in PH and RV failure**
        i. **Increased RV afterload and right to left shunting through PFO**
4. **Peri-operative Evaluation and Management**
    a. **Pre-op history and physical**
        i. **Symptoms and/or history of PH**
        ii. **EKG, echo in patients with risk factors for PAH**
    b. **Assessment of Operative Risk**
        i. **High, intermediate, low risk procedures/surgeries**
    c. **Multidisciplinary planning for patients with established PH/PAH and RV dysfunction**
        i. **PH specialist, surgeon, and anesthesiologist**
        ii. **Pre-op echo and hemodynamic assessment**
    d. **Pre-operative hemodynamic optimization**
        i. **Hemodynamic goals**
        ii. **Strategies**
5. **Operative Management**
    a. **Monitoring**

- **i. Hemodynamic**
  1. **Central line**
  2. **PA catheter**
- **ii. TEE**
- **iii. Blood Gas/Ventilator Monitoring**

**b. Airway management and ventilation**

- **i. Avoid pulmonary vasoconstriction by avoiding**
  1. **High PEEP (>15 mmHg)**
  2. **Hypoxemia**
  3. **High inspiratory pressure (>30 mmHg)**
  4. **Hypercapnia**
  5. **Acidosis**
- **ii. Promote pulmonary vasodilation**
  1. **Improve oxygenation**
  2. **Permissive hypocapnia**
  3. **Optimal ventilator tidal volume**
  4. **Mild alkalosis**

**c. Inotrope, Inodilator, and Pressor Use**

**d. Pulmonary vasodilator therapies**

- **i. Inhaled nitric oxide**
- **ii. IV nitroprusside, nitroglycerine, nesiritide**
  1. **PH related to left heart disease**
  2. **Tips/Pearls**
- **iii. Epoprostenol IVor treprostinil IV/SQ**
  1. **Appropriate candidates**
  2. **Warnings/precautions**
- **iv. Inhaled prostacyclin analogues**
  1. **Appropriate candidates**
  2. **Warnings/precautions**
- **v. Oral PDE 5 Inhibitors**
  1. **Sildenafil and dosing**
  2. **Others**

**e. Special Operative Case Considerations**

- **i. Orthopedics**
- **ii. Laparoscopy**
- **iii. Thoracic Surgery**
- **iv. Obstetrics**

**6. <u>Post-operative Management of PH</u>**

**a. Post-op Monitoring in ICU**

- **i. PA catheter**
- **ii. Central line**
- **iii. Role of echo**

**b. Optimize Preload**

- **i. Hypervolemia**
  1. **Diuretics**
  2. **AVP antagonists**
  3. **Ultratifiltration**

   - **ii. Hypovolemia**
     1. **Passive leg raise**
     2. **Fluid bolus**
- **c. Optimize Afterload**
   - **i. Respiratory/vent management**
     1. **Avoid hypoxia, hypercapnia, high PEEP**
     2. **Promote optimal oxygenation, hypocapnia, PEEP 5-10 or less**
   - **ii. Pulmonary vasodilators**
     1. **iNO**
     2. **Nitrates**
     3. **Prostacyclin analogues**
     4. **PDE 5 inhibitors/sildenafil**
- **d. Optimize RV Performance**
   - **i. Maintain systemic arterial pressure**
   - **ii. Use of inotropes, inodilators, pressors**
   - **iii. Treat arrhythmias**
- **e. Transition from Acute to Chronic PH Therapies**

Selected References and Resources

[61-67]


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## XI. Transplantation in Patients with Pulmonary Hypertension

Learning Objectives

1) Understand the indications, timing, LAS score, and outcomes of Lung transplantation for pulmonary arterial hypertension
2) Learn bridging strategies for pulmonary hypertension patients listed for lung transplantation
3) Review the surgical considerations and intra-operative management of PAH patients undergoing lung transplantation

4) Review the indications, considerations, and outcomes of transplantation for congenital heart disease
5) Learn the pathophysiology and the risks, outcomes, and hemodynamic criteria for liver transplantation with pulmonary hypertension
6) Understand the use of advanced PAH therapies and their risks and efficacy in portopulmonary hypertension

1. **<u>Lung Transplantation for Pulmonary Arterial Hypertension</u>**
   a. **Indications**
   b. **Timing of listing**
   c. **Outcomes after transplantation**
      i. **Bilateral vs single lung transplant**
   d. **LAS Score**
      i. **Bias against PAH**
      ii. **LAS score exception points for PAH**
         1. **Criteria and exception score**
         2. **UNOS Board Review Exception Request**
   e. **Bridging Strategies for PAH Lung Transplant Candidates Failing Medical Therapy**
      i. **V-A ECMO/ECLS**
      ii. **Novalung**
      iii. **Other**
   f. **Intra-operative Management and Surgical Considerations for PAH Patients Undergoing Lung Transplantation**
      i. **Surgeons perspective**
      ii. **Anesthesiologists perspective**
2. **<u>Transplantation for Congenital Heart Disease</u>**
   a. **Eisenmenger Syndrome**
      i. **Epidemiology and Outcomes**
      ii. **Bilateral Lung Transplant/heart repair**
      iii. **Heart-Lung Transplantation**
   b. **Complex Congenital Heart Disease**
      i. **Outcomes**
      ii. **Considerations for Transplant Listing and Timing**
         1. **More palliative procedures versus transplantation/vascular repair**
         2. **Number of prior surgeries**
         3. **Overall clinical status and comorbidities**
3. **<u>Bridging Strategies to Transplantation in Advanced Lung Disease and PH</u>**
   a. **V-A ECLS, Central vs Peripheral**
      i. **Centrimag**
      ii. **Maquet Cardiohelp**
   b. **V-V ECMO, Peripheral**
      i. **Avalon catheter**
      ii. **Centrimag**
      iii. **Maquet Cardiohelp**
4. **<u>Portopulmonary Hypertension and Liver Transplantation</u>**
   a. **Pathophysiology of Portopulmonary Hypertension**

- **b. Risks and Outcomes of Liver Transplantation with Portopulmonary Hypertension**
- **c. Hemodynamic definitions and criteria for liver transplantation**
  - **i. Portopulmonary Hypertension definition**
  - **ii. Hemodynamic criteria for liver transplantation with PoPH**
  - **iii. Other hemodynamic profiles in advanced liver disease and impact on liver transplantation**
    1. **Pulmonary venous hypertension**
       - **a. High PA mean and PCW pressures, high CO, normal PVR- no increase in peri-op moratality**
    2. **Mixed Pre- and Post-capillary PH**
       - **a. High PA mean and PCWP, high CO, increased TPG, PVR < 3- acceptable outcomes with liver Tx**
- **d. Treatment of PoPH with advanced PAH Therapies**
  - **i. Clinical trial evidence-PORTICO**
  - **ii. PAH drugs- risks/benefits/preferred agents**
  - **iii. Efficacy in achieving liver transplant candidacy**
  - **iv. Outcomes without liver transplantation**

Selected References and Resources

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# Addendum

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