International Society for Heart and Lung Transplantation

(ISHLT)

Pulmonary Hypertension
Core Competency Curriculum

(ISHLT PH CCC)

FIRST EDITION

The Educational Leadership of the
ISHLT Pulmonary Hypertension Council

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Addendum
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 pulmonary vasodilator therapies
5) To understand the risks of misclassification of PH and misuse of pulmonary vasodilator therapies
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. Mixed/Reactive/Non-reactive/“out of proportion” PH
   c. Clinical Classification
      i. Current WHO 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. HFrEF 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. Very poor survival with PoPH (French, REVEAL)
   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
   iii. Assessment of the RV function
       1. Imaging
           a. Echo
           b. MRI
           c. CT
       2. Invasive hemodynamics
   iv. Management of RV function and failure in PH
       1. Preload reduction - diuretics
       2. Afterload reduction - pulmonary vasodilator therapies
       3. Contractility - digoxin, avoid negative inotropic agents
       4. Other - aldosterone antagonism

4. Physician Specialties Currently Treating PH
   a. Pulmonologists
   b. Cardiologists
   c. Anesthesiologists
   d. Cardiac and Thoracic surgeons (Transplantation, conventional surgery)
   e. Primary Care Providers
   f. Rheumatologists

5. Recognition of the Need for PH Training and Core Competencies
   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 venous hypertension (Group 2 PH) misclassified as PAH and treatment with PH therapies that may worsen HF and symptoms
ii. Group 3 PH misclassified as PAH and treated with vasodilators that may worsen V/Q mismatch and hypoxemia

iii. PAH misclassified as pulmonary venous hypertension
   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. Bosentan and ambrisentan
   2. FDA 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. Epoprostanol, treprostinil, iloprost
   2. FDA approved indications
   3. 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. Phosphodiesterase type 5 inhibitors
   1. Sildenafil and tadalafil
   2. FDA approved indications
   3. Potential/theoretical risks in non-PAH PH
      a. Hypotension
      b. V/Q mismatch and hypoxia (systemic administration, more theoretical)
      c. Safe for most conditions, may improve oxygenation in ILD and improve hemodynamics in Group 2 PH

Selected References and Resources

[1-5]

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 historic risk factors for pulmonary hypertension
3) To know common physical findings in pulmonary hypertension and distinguishing features of pulmonary arterial and pulmonary venous 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-synecope/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  
i. Connective tissue disease  
ii. Family history of PAH  
iii. HIV infection  
iv. Portal Hypertension  
v. 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. Common Presenting Scenarios in PH  
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. Diagnostic Testing  
a. Echocardiography  
i. Utility and limitations  
ii. Required measures  
iii. TR jet velocity and accuracy of PASP estimate  
iv. Shunt study
v. Ventricular interdependence

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. Ventilation-Perfusion Scan
   i. CT pulmonary angiogram
   ii. Invasive 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
   v. Common mistakes and pitfalls
   vi. When to perform left heart catheterization to measure LVEDP
   vii. 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. Prognostic value of exercise testing in PH
   iv. 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, angiopoietins

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

Selected References and Resources
[2, 6-16]


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 discuss prognosis in PH based on etiology
4) To learn baseline prognostic factors in PAH
5) To understand the value of functional assessment and exercise capacity at baseline and follow-up
6) Learn the value of invasive and non-invasive hemodynamic variables, role of imaging, and use of prognostic equations in PAH
7) To understand the classes of drugs approved to treat PAH, timeline of FDA approval, 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 understand the physiologic/hemodynamic effects of atrial septostomy in PAH, risks, patient selection, and the evidence supporting its use in PAH

11) 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

12) 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

13) Understand the role of palliative care and learn the steps in forming a palliative care team for PAH patients

14) Learn how to utilize the ISHLT registry report and resources

1. **Pathophysiology of Pulmonary Arterial Hypertension**
   a. **Pulmonary Arterial Pathology**
      i. Pulmonary artery vasoconstriction
      ii. Pulmonary artery smooth muscle cell hypertrophy and hyperplasia
      iii. Pulmonary artery adventitial changes
      iv. Plexogenic lesions
      v. In situ thrombosis
   b. Right ventricular dilatation and failure
   c. Ventricular interdependence

2. **Epidemiology of Pulmonary Arterial Hypertension**
   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. **Survival in Pulmonary Arterial Hypertension**
   a. Idiopathic/Familial PH (formerly PPH)
      i. NIH, REVEAL, France, other cohorts
b. Survival in PAH based on etiology
   i. REVEAL
   ii. French Registry
   iii. Pulmonary Hypertension Connection
   iv. Other cohorts

4. Prognostic Factors in PAH
   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. Prognostic equations in PAH
      i. NIH
      ii. REVEAL

5. Treatment of PAH
   a. Adjunctive Therapies
   b. Calcium Channel Blockers
      i. Indications
      ii. Drug choice and dosing
      iii. Follow-up
   c. 3 Classes and Pathways of PAH Therapies
   d. Timeline of FDA Approval of Currently Available PAH Therapies
   e. Pivotal Trials
   f. Common side effects of PDE5I, ERA, Prostanoid Therapies
   g. Guideline based treatment algorithm
   h. Guideline based follow-up
1. Clinical follow-up
   ii. Objective measures
      1. Non-invasive
      2. Hemodynamics
   i. Combination Therapy
   i. Clinical Trials

6. Lung Transplantation
   a. Indications in PAH
   b. Timing of Referral for PAH
   c. Survival after Lung Transplantation for PAH

7. Atrial Septostomy
   a. Procedure
   b. Physiologic/Hemodynamic Effects
   c. Risks
   d. Indications/Patient Selection
   e. Evidence

8. End-stage PAH disease
   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. How to Utilize the ISHLT Registry Report and Resources

Selected References and Resources

[17-30]


IV. Pulmonary Hypertension in 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) Learn the diagnostic evaluation of patients with suspected Group 2 PH
4) To review the hemodynamics and understand the fundamental differences between Group 1 and Group 2 PH
5) To learn the pathophysiology of pulmonary hypertension in left heart disease, including pulmonary vascular remodeling and PH out of proportion
6) To review therapeutic options based on clinical trial data in Group 2 PH
7) To discuss the diagnostic and therapeutic challenges of mixed PH classification patients
8) To learn the risks and management of PH in heart transplant candidates with nonreactive/fixed PH
9) Learn strategies to manage PH and right heart failure in patients undergoing LVAD implantation
1. **Overview of Pulmonary hypertension due to left heart failure**  
   a. Systolic, diastolic, valvular left heart disease  
   b. Cor triatriatum, atrial myxoma with atrial obstruction  

2. **Epidemiology and Prognostic Significance of PH in Left Heart Disease**  
   a. HFrEF and PH  
      i. Ischemic cardiomyopathy  
      ii. Dilated cardiomyopathy  
   b. HFrEF and PH  
      i. Hypertensive heart disease  
      ii. Coronary heart disease  
      iii. Diabetic cardiomyopathy  
      iv. Hypertrophic cardiomyopathy  
      v. Restrictive cardiomyopathy  
      vi. Constrictive pericarditis  
   c. PH with aortic and mitral valve disease  
      i. AS/AR  
      ii. MS/MR  
      iii. Persistent/residual PH after corrected valvular defect  

3. **Diagnosis of Group 2 PH**  
   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 with gadolinium  
      i. Infiltrative cardiomyopathies  
      ii. Complex congenital heart disease
e. Evaluation for CAD
   i. Indications
   ii. Non-invasive stress testing
      1. Consider timing before catheterization
   iii. Coronary angiography
f. When should heart catheterization be considered
   i. Symptoms not responding to treatment of LHD
   ii. PH with preserved EF unless mod-severe diastolic dysfunction by echo
   iii. PH with afib and normal EF

4. Hemodynamic Definitions and Classification of PH due to Left Heart Disease
   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. Mixed/Reactive Pulmonary Hypertension from LHD
         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
   b. When to consider provocative maneuvers during catheterization
      i. Fluid challenge
      ii. Exercise
      iii. Vasodilator testing
         1. Nitroprusside vasoreactivity testing in heart transplant/VAD candidates
   c. When to consider left heart catheterization
      i. LVEDP direct measurement
         1. Routine to confirm elevated PCWP
         2. Unable to wedge PA catheter
         3. Blood gas from wedged PA catheter not fully saturated
      ii. Simultaneous LHC/RHC hemodynamics
      iii. Coronary angiography

5. Pathophysiology of PH in Left Heart Disease
   a. Passive pressure elevation
   b. Pulmonary Vasoconstriction
   c. Pulmonary vascular remodeling with chronic pulmonary venous hypertension

6. Treatment of PH Related to Left Heart Disease
   a. Diuretics
   b. Evidence-based therapy for HFpEF
   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
      3. Potential therapies/off-label use of PDE5I
      4. Future/ongoing trials of LHD

Selected References and Resources
[31-36]


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
To discuss the challenges of mixed PH classification patients

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

2. **Epidemiology and Prognostic Significance of PH in Lung Disease and/or Hypoxemia**
   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. **Pathophysiology of PH in Group 3 PH**
   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. **Diagnostic Evaluation of PH Related to Lung Disease and/or Hypoxemia**
   a. ABGs
   b. Pulmonary Function Testing
      i. DLCO
      ii. FVC, FEV1, FEV1/FVC ratio
      iii. FVC/DLCO ratio in ILD and PH
   c. Computed Tomography
      i. HRCT Chest without Contrast
         1. Evaluate for ILD
      ii. Volumetric CT

5. **Treatment of PH Related to Lung Disease and/or Hypoxemia**
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. 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. Challenges in Mixed PH Etiologies  
  a. Scleroderma lung disease  
    i. Is it Group 1 or Group 3 PH?  
    ii. FVC/DLCO ratio  
    iii. Management considerations  
  b. PH “out of proportion” to lung disease

Selected References and Resources

[37-44]

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

1. Epidemiology of CTEPH
   a. Incidence/prevalence (proximal operable disease vs distal disease)
   b. Survival
   c. Registry data from Europe
2. Pathophysiology of PH in Group 4 PH
   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. Diagnostic Evaluation of PH Related to CTEPH
   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. Treatment of CTEPH
a. Referral to center of excellence  
b. Oxygen Supplementation  
c. Pulmonary Thromboendarterectomy Surgery  
   i. Indications/contraindications  
   ii. Outcomes  
d. PAH Specific Therapies  
   i. Clinical Trial Evidence  
      1. Riociguat and PATENT Trial  
   ii. Recurrent/persistent PH after PTE surgery  
   iii. Non-surgical candidates  
   iv. Use as “bridge to surgery”  
e. Balloon Pulmonary-Artery Angioplasty  
   i. Patient selection

Selected References and Resources

[45]


**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. **Review of PH with unclear/multifactorial mechanisms**

   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’ (PVOD by pulmonary vein 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. **Diagnostic Evaluation of PH Related to unclear/ multifactorial mechanisms**

   a. R/O Group I-IV
   b. Clues based on History, CBC, TFTs, CXR, other chest imaging

3. **Treatment of Group 5 PH**

   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]


**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
Currently enrolling Clinical Trials in PAH

- GRIPHON
- AMBITION
- FREEDOM-Ev
- AMB and TAD in PAH-SSc
- Others

Recently Completed Clinical Trials

- Mono and combination trials

Potential New Targets for Therapeutics

Novel Trial Design

Ethics in Clinical Trials for an Orphan Disease

Currently Enrolling Clinical Trials in Secondary PH

- iNO study in Group 3 PH
- Riociguat in ILD-PH
- Riociguat in CTEPH-LTE

Selected References and Resources

[50-55]


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. **Identify and treat underlying precipitating factors**  
a. Dietary indiscretion, infection, anemia/erythrocytosis, dysrhythmia, thyroid disorder, pulmonary embolus

2. **Restore oxygenation**  
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. **Restore vital organ perfusion**  
a. Pulmonary vasodilators  
   i. Inhaled NO/epoprostenol/Other inhaled vasodilators  
   ii. IV epoprostenol (candidates for chronic IV epo therapy)  
   iii. 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. **Treat volume overload**  
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

5. **Stabilization Achieved**  
a. Wean NO with IV epoprostenol or troprostnil  
b. Wean IV inotropic agents  
c. Optimize chronic therapies

6. **Refractory/Unstable cases (Bridge to Lung Transplantation for Candidates)**  
a. IV epoprostenol + other pulmonary vasodilators  
b. Inotropic support (B-adrenergic agonists, digoxin, diuretic therapy)  
c. ECLS (V-A ECMO/ECLS)  
d. Percutaneous atrial septostomy

7. **Unstable and/or refractory cases (NOT a candidate for Lung Transplantation)**  
a. Palliation of symptoms  
   i. Oxygen  
   ii. Diuretics  
   iii. Inotropes home infusion  
   iv. Liberal use of narcotics  
b. Hospice
Selected References and Resources

[5, 56-60]


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
         1. High PEEP (>15 mmHg)
2. Hypoxemia
3. High inspiratory pressure (>30 mmHg)
4. Hypercapia
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 IV or 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. Post-operative Management of PH
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. Ultratiffiltration
   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]


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. **Lung Transplantation for Pulmonary Arterial Hypertension**
   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. **Transplantation for Congenital Heart Disease**
   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. **Bridging Strategies to Transplantation in Advanced Lung Disease and PH**
   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. **Portopulmonary Hypertension and Liver Transplantation**
   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 mortality
      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
   ii. PAH drugs - risks/benefits/preferred agents
   iii. Efficacy in achieving liver transplant candidacy
   iv. Outcomes without liver transplantation

Selected References and Resources

[26, 27, 68-73]


Addendum
First Edition Date

Reference List


