RTBoardReview
Simulation 31 – 42 Year-Old Woman with Unexplained Dyspnea
Condition/Diagnosis: Idiopathic Pulmonary Hypertension (Group I/Class III Symptoms)

Take-Home Points:

Pulmonary hypertension is a clinical finding, not a disease. It includes several conditions characterized by a mean pulmonary artery pressure (mPAP) > 25 mm Hg at rest or > 30 mm Hg with exercise. These conditions fall into 5 groupings: Group I (including pulmonary arterial hypertension or PAH, congenital heart disease, and persistent pulmonary hypertension of the newborn or PPHN); Group II (pulmonary hypertension associated with left heart disease); Group III (pulmonary hypertension associated with lung disease, e.g., COPD); Group IV (pulmonary hypertension cause by thrombi/emboli); and Group V (miscellaneous causes, such as connective tissue diseases).

Assessment/Information Gathering

Symptoms

- You should suspect pulmonary hypertension is any patient with *unexplained* dyspnea, especially on exertion. Dyspnea is unexplained either if it occurs with
  - no signs of specific heart or lung disease
  - signs of lung or heart disease, but is more severe that the condition would suggest
- Other symptoms include fatigue, chest pain and dizziness/syncope (sometimes only with activity)

Based on symptoms, there are four *functional* classes of pulmonary hypertension (World Health Organization/WHO classification; similar to the NY Heart Association classification of heart failure):

Class	Description
I	Those for whom ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
II	Those who are comfortable at rest but for whom ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
III	Those who are comfortable at rest, but even minimal activity causes undue dyspnea or fatigue, chest pain, or near syncope.
IV	Those experiencing dyspnea and/or fatigue even at rest, typically manifesting signs of right-heart failure, and unable to carry out any physical activity without symptoms

Physical Signs

- Vital signs/SpO2
  - tachycardia at rest
  - reduced pulse pressure
  - desaturation (> 3-4%) with exertion
- Auscultation
  - Heart sounds:
    - loud pulmonary component of the 2nd heart sound (P2)
    - pansystolic murmur indicating tricuspid regurgitation
    - diastolic murmur indicating pulmonic insufficiency
    - Lung sounds - unremarkable unless left heart (Group II) or pulmonary disease (Group III)
- Inspection (signs of right heart failure in advanced disease):
  - jugular vein distention
  - hepatomegaly
  - peripheral edema
  - ascites
  - cool extremities
  - central cyanosis

Recommending Diagnostic Tests

- Pulmonary artery (PA) catheterization (the ***gold standard*** for diagnosis)
  - Confirms presence of hypertension (mPAP > 25 mm Hg at rest) and its severity (mild: < 35 mm Hg; moderate: 35-45 mm Hg; severe > 45 mm Hg)
  - Can differentiate PAH (Group I) from other causes such as LVF, e.g.
    - PAH: normal PCWP (<15 mm Hg), ↑PVR (>3 mm Hg/L/min or >240 dynes-sec/cm^5)
    - LVF: ↑ PCWP (>15 mm Hg), normal PVR (<3 mm Hg/L/min or <240 dynes-sec/cm^5)
  - Can ID patients with PAH who can be treated with Ca-channel blockers (vasodilator test)
    - patient administered IV epoprostenol or inhaled nitric oxide
    - positive response: mPAP decrease ≥10 mm Hg, to <40 mm Hg
- Imaging tests
  - Echocardiography (for screening and diagnosis); findings can include:
    - right ventricular systolic pressure ≥40 mm Hg (= PA systolic if no outflow obstruction)
    - enlarged, 'D-shaped' RV, septal bowing into the LV during systole
    - tricuspid regurgitation
    - dilated RA and vena cava
    - pericardial effusion
  - Chest CT
    - enlarged main pulmonary artery (diameter > 29 mm)
    - may identify thrombi within the pulmonary arteries (Group IV)
  - Chest X-ray
    - not especially helpful in identifying early stage PAH
    - can help identify Group II, III or V processes
    - in advanced disease: enlargement of the central pulmonary arteries, cardiomegaly
- ECG (findings usually seen late in disease process ; can help exclude other diagnoses)
  - Right-ventricular hypertrophy/right-axis deviation
  - Right-atrial enlargement
  - Right bundle-branch block
- Pulmonary function tests/sleep studies - to identify or rule out Group III conditions as cause
- Exercise Tests
  - 6-min-walk test
    - 6MWD < 330 m associated with higher mortality in PAH patients
    - helps monitor patient progress and evaluate response to therapy
  - Cardiopulmonary Exercise Test
    - can be difficult for patients to perform (due to debilitating dyspnea)
    - VO2max < 10 mL/kg/min predicts survival
- Laboratory Tests
  - Serum troponin (associated with RV overdistension and/or ischemia)
  - BNP (correlates with PVR, cardiac output, and functional class of patients with PAH)
  - Other tests specific to suspected conditions, e.g., d-dimer for pulmonary embolism

Treatment/Decision-Making

Treatment for pulmonary hypertension varies by condition and functional classification. The following table outlines the different treatment strategies according to condition grouping. The remainder of this prep sheet focuses on Treatment/Decision Making for pulmonary arterial hypertension/PAH (Group I).

Group	Common Treatment Approaches
I (PAH, CHD, PPHN)	• Pulmonary vasodilators • Atrial septostomy • Lung/heart-lung transplantation
II (Left heart failure)	• LVF: Diuretics, beta blockers, ACE inhibitors • Valve disease: repair/replace
III (Lung disease)	• COPD/ILD: O2 therapy • Sleep disorders: CPAP/BiPAP
IV (Thrombo-embolic disorders)	• Anticoagulants/thrombolytics • Pulmonary thromboendarterectomy
V (Miscellaneous)	• Treatment by specific cause

For patients with pulmonary arterial hypertension (PAH) recommend:

- pulmonary vasodilator therapy (see following table)
- diuretics as appropriate (to reduce symptoms of right ventricular failure)
- oral thrombolytic therapy, e.g., warfarin (if PAH is idiopathic)
- O2 therapy for hypoxemia
- influenza and pneumococcal vaccination
- lifestyle modifications, e.g. aerobic exercise, sodium-restricted diet

The following table summarizes current categories and administration routes of pulmonary vasodilators.

Category/Agent	Available Routes
Calcium Channel Blockers	
Diltiazem (Cardizem)	Oral
Nifedipine (Procardia)	Oral
Prostacyclins	
Epoprostenol (Flolan)	IV, Inhalation (off-label)
Treprostinil (Remodulin)	IV, SQ (continuous)
Treprostinil (Tyvaso) solution	Inhalation
Treprostinil (Orenitram) tabs	Oral
Iloprost (Ventavis)	Inhalation
Phosphodiesterase-5 (PDE-5) Inhibitors	
Sildenafil (Viagra, Revatio)	Oral
Tadalafil (Adcirca)	Oral
Vardenafil (Levitra)	Oral
Endothelin Receptor Antagonist (ERAs)	
Bosentan (Tracleer)	Oral
Ambrisentan (Letairis)	Oral
Macitentan (Opsumit)	Oral
Guanylate Cyclase (sGC) Stimulators	
Riociguat (Adempas)	Oral

Recommend:

- An *oral agent* for patients with WHO Class II or III symptoms (note: Ca channel blockers are indicated to treat PAH *only if the patient has a positive response to the vasodilator test*; they are contraindicated in patients with right heart failure or those who are hemodynamically unstable)
- *Combination therapy* using oral or oral + inhaled agents with different mechanisms of actions for patients whose symptoms persist when receiving a single drug
  - ambrisentan (an ERA) + tadalafil (a PDE-5 inhibitor) is recommended as 1st line therapy for newly diagnosed patients with group I PAH and WHO Class II or III symptoms
  - the FDA warns against combining PDE-5 inhibitors and sGC stimulators (due to an unfavorable safety profile)
- *Continuous parenteral therapy* (i.e., Flolan, Remodulin) for patient with severe symptoms (WHO functional Class IV) or those with WHO Class III disease that progresses despite treatment with oral/inhaled agents.

What about nitric oxide? Inhaled nitric oxide (INO) is appropriate for use only in the acute care setting with very limited indications. *It is not used to manage patients with chronic pulmonary hypertension*. Currently INO is approved only for the treatment of term and near-term neonates (≥34 weeks) with hypoxemic respiratory failure (PaO2 <100 torr on FIO2 = 1.0 and/or an oxygenation index >25) associated with pulmonary hypertension (PPHN). Common "off-label" uses of INO (for which evidence of effectiveness is lacking or inconclusive) include the following:

- prevention of bronchopulmonary dysplasia/chronic lung disease in infants
- management of pulmonary hypertension after cardiac surgery in infants and children with congenital heart disease
- treatment of pulmonary hypertension associated with ARDS in children and adults
- treatment of pulmonary arterial hypertension/acute right ventricular failure in adults
- treatment of sickle cell crisis

Follow-up Resources

Standard Text Resources:

Hargett CW & Tapson VF. (2012). Pulmonary vascular disease (Chapter 37) in Hess DR et al (Eds) *Respiratory care: Principles and practices* (2nd ed). Sudbury, MA: Jones & Bartlett.

Tonelli AR et al. (2013). Pulmonary vascular disease (Chapter 26) in Kacmarek RM et al *Egan's Fundamentals of Respiratory Care* (10th ed). St. Louis: Elsevier-Mosby.

Useful Web Links

Dweik RA. (2011). *Pulmonary Hypertension*. Cleveland Clinic Center for Continuing Education. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/pulmonary-hypertension/

Galiè N et al. (2013). Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*, 62, D60–72. http://content.onlinejacc.org/article.aspx?articleid=1790601

Hill NS, Preston JR & Roberts KE. (2015). Inhaled therapies for pulmonary hypertension. *Respir Care*, 60, 794-802. http://rc.rcjournal.com/content/60/6/794.full.pdf

Levine DJ. (2006). Diagnosis and management of pulmonary arterial hypertension: Implications for respiratory care. *Respir Care*, 51, 368-381. http://rc.rcjournal.com/content/51/4/368.full.pdf

Oudiz RJ. (2015). *Primary Pulmonary Hypertension*. EMedicine/Medscape. http://emedicine.medscape.com/article/301450-overview

Siobal MS. (2007). Pulmonary vasodilators. *Respir Care*, 52, 885-899. http://rc.rcjournal.com/content/52/7/885.full.pdf