AHD: Pulmonary Hypertension

Facilitator Guide

Case #1

Ms. Alto is a 48 yo F with a history of depression who presents to your medicine clinic for PCP establishment. She hasn't seen doctor since college but decided to come because her shortness of breath. She been having worsening shortness of breath on exertion for the past 6 months. In the past, she walked up the several flights of steps to her apartment with ease but now she has to stop several times to catch her breath. She has no associated cough, sputum production, or wheezes. She has never smoked.

Home Meds: Sertraline 50 mg qday, PRN ibuprofen

Yes, this is the pulmonary hypertension AHD so it's already on the differential diagnosis. What else is in the differential diagnosis? What further information do you want to know?

This is a chronic process so ddx should include chronic, progressive processes. Differential diagnosis is very broad and includes cardiac (arrhythmia, valvular, HF, restrictive cardiomyopathy, pericardial disease), pulmonary (asthma, restrictive lung disease, ILD, PH, chronic pulmonary emboli), metabolic (hypothyroidism), psychiatric (depression/anxiety), anemia, neuromuscular disease, obesity.

Further information → further characterization of symptoms, hx of clot/DVT/PE, FMH, GU hx, assess depression (may contribute to HPI), social hx (sexual [HIV risk factors], drug & occupational exposures), signs/sx of sleep disorder

- *Denies any orthopnea. She occasionally has some chest pressure with walking the steps but it is very inconsistent and resolves spontaneously. Denies any LE swelling, palpitations, weight gain/loss, syncope, heat/cold intolerance*
- *She denies joint pain but reports that her finger sometimes hurt when she goes into the cold weather. She has to wear mittens frequently in the winter months*
- *FMH - DM and HTN*
- *Menstrual history - regular periods without heavy bleeding*
- *Assess her depression, consider a PHQ9 - Her depression is well controlled*
- *Drug use? She denies any IVDU or inhaled drug use, including cocaine and methamphetamine. Denies OTC diet pills (phentermine, aminorex linked to PH)*
- *Occupation? She works as a paralegal for law firm downtown*
- *Sexual Hx? Sexually active with multiple male partners, has IUD, inconsistent condom use*
- *Sleep Hx? STOP-BANG. Her roommate does NOT report snoring, no morning HA, no daytime somnolence*

Exam:
T: 98 HR: 80 BP: 125/65 RR: 16 Oxygen saturation: 98% on RA Wt: 140 lbs (63.5 kg)
Gen: young Caucasian woman, AAOx3.
HEENT: Moist oral mucosa. No lymphadenopathy

Neck: No JVD, trachea midline
Heart: RRR, normal S1/S2. No murmurs, rubs or gallops.
Lungs: CTAB, no wheezing or crackles noted.
Abd: + BS. Soft. NTND
Ext: Puffy, nonpitting edema of her fingers with associated skin thickening. No LE edema
Neuro: Alert and Oriented to person, place, time and situation. No focal neurologic deficits.

Where do you start with your workup?

Labs/Studies:

135 | 101 | 11 / 13
---------- 100 6.1 >-----< 225
4.1 | 26 | 0.7 \ 40

ANA titer: positive
Anti-Scl-70: positive
UA: normal
EKG: NSR, normal axis, no ST changes

CXR: normal lung volumes, no acute cardiopulmonary process

TTE → What info do they want? (LV function, RV function, hypertrophy/dilation, valves, PASP pressure) Important to teach to start with a TTE (LV dysfunction is #1 cause of PH) instead of shotgun w/u

- *Result: LVEF 60%, RV function is normal. No LA dilation. RV appears hypertrophied. There is no valvular regurgitation or stenosis. PASP estimated at 45 mmHg*

What is the most likely diagnosis? What are the common causes of PH and how are they organized?

TTE screens positive for pulmonary hypertension (PASP > 35-40 mmHg). Over 85% of patients present with exertional dyspnea with often 2+ years of sx, delay in diagnosis.

WHO Groups → organize PH by etiology of the pulmonary hypertension (PH is NOT equivalent to PAH)

WHO GROUP	*ETIOLOGY*	*SOME SPECIFIC CONDITIONS*
I	*Pulmonary Arterial Hypertension (PAH)*	*Idiopathic, drug/toxin exposure (methamphetamine, cocaine), HIV, congenital heart disease, portal HTN, connective tissue disease (Scl, lupus), PVOD*
II	*Left Heart Disease*	*HFrEF, HFpEF, CAD, aortic/mitral valvular disease, restrictive CM*
III	*Lung Disease*	*COPD, ILD, OSA*
IV	*Chronic Thromboembolic Pulmonary Hypertension*	*CTEPH, angiosarcoma of pulmonary artery, pulmonary arteritis*
V	*Unclear Mechanism*	*Sarcoidosis, sickle cell anemia, chronic hemolytic anemia, fibrosing mediastinitis, etc.*

Our patient has signs and labs consistent with systemic sclerosis, thus concerning for in Group I (PAH)

Ms. Alto returns to clinic one week later. She saw the results of the TTE on MyChart and is concerned about “elevated pulmonary pressures.” She continues to have DOE, otherwise no changes.

What are the next steps in her workup?

PFTs – recommended, decreased DLCO shown to have high sensitivity for predicting PAH in Scl patients, test rules out obstructive and restrictive lung disease

HRCT – recommended in all, ensure no concurrent ILD

V/Q scan –recommended in all patients in PH workup even if no hx of PE/DVT due to underdiagnosed CTEPH rates, gold standard screening test for CTEPH

6-minute walk test – gets baseline sx burden, can also be used to track changes in future (for monitoring or changes with treatment, etc.)

Serum BNP – elevations predictive of PH in some conditions, higher level consistent with poor prognosis

Polysomnography – only if there is clinical suspicion for sleep disorder, OSA

HIV, UDS, rheumatologic & SCD workup – ONLY if clinical suspicion, risk factors, or FMH warrants

Ms. Alto gets PFTs, which are normal aside from a mildly decreased DLCO. HRCT of chest is unremarkable aside from an enlarged pulmonary artery. V/Q scan show no ventilation-perfusion mismatch. Serum BNP was mildly elevated.

What is needed to confirm Ms. Alto's diagnosis?

All signs continue to point to Scl-related PAH. The diagnosis of PAH <u>REQUIRES</u> a RHC

TEACHING POINT: not all dx of PH require a RHC. If patient has a clear history and signs of left heart disease or chronic pulmonary disease, does NOT need RHC to be given dx of pulmonary hypertension

What do you expect it to show? What information you would like to know from the procedure?

Expect: elevated pulmonary pressures, low/normal wedge, elevated pulmonary vascular resistance

Diagnosis of PAH (on RHC) = mean PAP ≥ 20 mmHg + PCWP (wedge) ≤ 15mmHg + PVR ≥ 3 Wood units

Pulmonary vasoreactivity? Short-acting vasodilator (NO, epoprostenol) is injected during RHC to assess if patient has vasoreactivity. If mean PAP decreases by >10 mmHg or to <40 mmHg w/o reduction in cardiac output = vasoreactive. Why important? Vasoreactive patients can be treated with CCBs

TEACHING POINTS: what do RHC look like for other conditions of PH? All similar to PAH except that LH disease has an <u>elevated</u> wedge pressure (PCWP is representative of LA pressure)

Table 1. Diagnostic Criteria and WHO Categorization of Pulmonary Hypertension[a]

	All Groups	Group 1	Group 2	Group 3	Group 4	Group 5
Description	Elevated pulmonary artery pressure	Pulmonary arterial hypertension	Pulmonary venous hypertension	PH due to hypoxemia	Chronic thromboembolic PH	Miscellaneous or multifactorial PH
Estimated prevalence[b]	Up to 10%-20% of the general population	15 cases per million overall, 6 cases per million for idiopathic PAH[c]	>3-4 million in the United States	20% in COPD patients with a prior hospitalization for COPD exacerbation, >50% in advanced COPD; 32%-39% in interstitial lung disease	0.5%-2% (up to 3.8%) in survivors of acute pulmonary embolism	Unclear
Diagnostic criteria[d]						
Mean PA pressure, mm Hg	≥25	≥25	≥25	≥25	≥25	≥25
PCWP or LVEDP, mm Hg		≤15	>15	≤15	≤15	≤15
PVR, dynes/s/cm^5		>240		>240	>240	>240

Abbreviations: COPD, chronic obstructive pulmonary disease; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization.
[a] WHO categorization of pulmonary hypertension is described in detail elsewhere.[3]
[b] Prevalence estimates were derived from other sources.[1,4-10]
[c] Worldwide prevalence of PAH due to schistosomiasis is not well defined; thus, the worldwide prevalence of PAH may be higher.
[d] Definitive diagnosis requires invasive hemodynamic testing. Pressures should be measured at end-expiration (not the digital mean) to minimize the effect of negative intrathoracic pressure on hemodynamic values, which is especially common in patients with parenchymal lung disease and morbid obesity (both of which cause large swings in intrathoracic pressure). Accurate PCWP position should be confirmed fluoroscopically and by checking PCWP saturation (confirming that it is equal to the systemic saturation). When in doubt, left heart catheterization should be performed to measure LV filling pressures directly.

Ms. Alto's RHC shows a mean PAP of 35 mmHg, PCWP of 10 mmHg, elevated PVR consistent with PAH, and negative for vasoreactivity.

What treatment options are available for Ms. Alto?

She needs to be referred to PAH specialist in a PAH-designated center (UCMC is one). These physicians will choose therapy based upon the patient's disease burden, prognosis, etc.

Disease burden breaks down into WHO functional classes – Class I is monitored; Class II, III, & IV need txt

- *Class I: no resulting limitation to physical activity*
- *Class II: slight limitation of physical activity, +SOB/fatigue/CP/near syncope w. ordinary activity*
- *Class III: marked limitation of physical activity, comfortable at rest, +SOB/fatigue/CP/near syncope w. less than ordinary activity*
- *Class IV: cannot carry out any physical activity w.o symptoms, +RHF, may have sx at rest*

Our patient has sx (SOB, CP, fatigue) with stairs (ordinary activity) → Class II

<u>Instead of specific regimens, focus on general classes of PAH medications</u>

- *Guidelines recommend certain agents with particular step-up escalation of therapy based on WHO class, goals of therapy, etc.*
- *Most agents are only FDA-approved and have proven benefit for Group I PAH*
- *Importantly, these medications can be harmful or no benefit in most other PH groups*

Drug Class	Examples	Mechanism of action
Phosphodiesterase-5 inhibitors	*Sildenafil (PO), tadalafil (PO)*	*Inhibits breakdown of cGMP which potentiates cGMP vasodilatory effects*
Endothelin receptor antagonists	*Ambrisentan (PO), bosentan (PO), macitentan (PO)*	*Inhibits endothelin-1 receptors on vascular smooth muscle → inhibit vasoconstriction*
Prostacyclin analogues/agonist	*Epoprostenol (IV), Iloprost (inhaled), Trepostinil (SC, IV), Selexipag (PO)*	*Stimulates intracellular production of cAMP in vascular smooth muscle → promoting vasodilation*
Guanylate cyclase stimulant	*Riociguat (PO)*	*Stimulates sGC → mimics NO to induce vasodilation*
Calcium channel blockers	*Nifedipine, amlodipine, diltiazem*	*Inhibit Ca+ channel → inhibit vasoconstriction → promote vasodilation*

Ms. Alto is referred to a PAH specialist and started on an appropriate therapy with improvement in symptoms. She returns to clinic 1 month later for general follow-up.

Given Ms. Alto's new diagnosis of PAH, is there any further recommended counseling?

Recommend supervised exercise activity

Maintain UTD immunization against influenza and pneumococcal pneumonia

Avoid pregnancy – if becomes pregnant, pre/post-natal care need to be a PH center

Avoid high altitude exposure – if air travel, supply O2 if needed to maintain SpO2>91%

Avoid non-essential surgery – all surgeries should be at PH center

Assume Ms. Alto had PH related to the another WHO Group, how would you then treat her pulmonary hypertension?

In general → treat the underlying condition!

Group II: goal-directed therapy for LH disease. I.e. diuretics, ACEi, BB, treat CAD, etc.

Group III: Depends on dx. Give inhalers, O2 (only proven mortality benefit in Group III PH), CPAP/BiPAP

Group IV: anticoagulation, refer for endarterectomy (only "curable" cause of PH)

Group V: treat underlying issue

Case #2

Ms. Ivey is a 56 yo F with a history of DM2, OSA on CPAP, PAH on multiple medications, who presents to the ED with worsening SOB with a productive cough. She has a history of progressive, idiopathic PAH that was diagnosed 1.5 years ago via RHC and she is currently being treated with PO ambrisentan, PO tadalafil, and IV epoprostenol (via portable pump and Hickman catheter). At baseline, she is typically comfortable at rest without SOB however, for the past 4 days she has been feeling SOB even while sitting in her chair. Her cough started 5 days ago, is productive with yellow sputum, and she has subjective fevers. She denies sick contacts. She lives at home by herself and has not been hospitalized in the last 6 months.

What are etiologies/things to consider when a patient with a diagnosis of PAH presents with worsening shortness of breath?

Infection – PNA, bacteremia, line infection (patient on chronic IV therapy), etc.

Adherence – Taking PAH meds consistently and appropriately? Using CPAP for OSA? Problems with pump or Hickman catheter for IV epoprostenol?

Progression of PAH – Need adjustment to PAH medications? Addition of new medications?

Metabolic – Anemia, hypothyroidism, renal failure (cardiorenal, AKI), pregnancy

Still at risk of things like PE, MI/CAD, CHF

Ms. Ivey reports that she has been adherent with all her medications and CPAP. She has not noticed any issues with her epoprostenol pump or Hickman catheter. She denies any chest pain, syncope, presyncope, heat/cold intolerance. She has been urinating normally without any change in frequency, dysuria, hematuria.

What further workup would you like to obtain? Any specific things to look for on exam?

Would be reasonable to order: CBC with diff, BMP, BNP, UA, Bcx, CXR, EKG, TTE
Exam: lung auscultation, assess for signs of RH strain/failure (JVD, LE edema, RV parasternal heave, ascites), examine pump and Hickman catheter

Exam:
T 100.1 P 102 BP 99/66 R 22 Sat 89% RA
GEN: Awake, alert. In mild distress
HEENT: No cervical adenopathy, no JVD, no bruits
CV: Tachycardic, regular rate, normal S1, loud S2, no murmur. No parasternal heave
RESP: labored, inspiratory crackles in the left base. No expiratory wheezing
ABD: Soft, non-tender, non-distended, no ascites
EXT: Trace bilateral edema of LE below ankles, warm distal extremities, palpable pulses
NEURO: AAOx3, no gross motor or sensory deficits
SKIN: Tunneled catheter (Hickman) present on right chest, no pain to palpation of catheter site, no surround erythema or discharge at insertion site. Pump appears to be functioning properly

Labs:
131 | 98 | 18 / 14 \ 11 / 300 Diff: 82% Neut
---------- 131 / 33 \
4 | 22 | 1.1 \
UA: no blood, trace protein, negative LE/Nitrite UPT: negative
BNP: 80
CXR: Prominent pulmonary arteries, LLL opacity with air bronchograms
EKG: Sinus tachycardia, normal axis, no concerning ST-T wave changes

Fill in admission orders below:

This patient has a PNA that is exacerbating her underlying PAH (worsening hypoxia). Important teaching points are to be cautious with excessive IVF, do NOT stop PAH meds, treat underlying cause, give supportive measures

Unit: *Stepdown*

Fluids: *reasonable to give IVF for soft BPs and mild Cr elevation. Give cautiously (consider preload strain on RH), isotonic IVF (limit to 250-500cc at a time)*

PAH Meds: *continue these! May need change IV epoprostenol from personal pump to bedside gtt (if patient confused, getting sedating medications, undergoing surgery, etc.)*

- *Do NOT hold PAH meds, change dosing or route (even if patient has soft BPs) without guidance from with PAH/pulm team and pharmacy*

Oxygen: *Nasal cannula O2, titrate to goal of >91% SpO2 per guidelines*

Consults: *Consult pulmonology if patient on IV therapy or concerned for progression of PAH. Pharmacy for IV prostacyclin medication. Palliative care recommended in CHEST guidelines to assist in management of disease burden and symptoms to improve QOL*

Treatment: *Ceftriaxone and azithromycin for CAP. Continue CPAP for OSA*

Case #3

Ms. Lannister is a 61 yo F with a history of HTN, hypothyroidism, PAH, who presents to the ED with worsening SOB and weight gain. She has a history of idiopathic PAH that was diagnosed 11 months ago via RHC and she is currently being treated with ambrisentan and tadalafil. Ms. Lannister can typically play with her grandchildren with mild SOB, but over the past month she has been getting more easily SOB even with simply walking to the bathroom. In addition, in the past week she has noticed about 12 lb of unintentional weight gain, predominantly in her lower extremities and abdominal swelling. She's having difficulty fitting into her pants. She came to the hospital this morning after she had an episode of palpitations and lightheadness requiring her to lie down after walking from the kitchen to the living room. She denies CP, cough, fever/chills, n/v. She denies any sick contacts.

Exam:
T 98.5 P 112 bpm BP 95/52 R 20 Sat 90% RA
GEN: Awake, alert but fatigued. In distress
HEENT: No cervical adenopathy, + JVD to mandible
CV: Tachycardic, regular rate, normal S1, loud P2, holosystolic murmur loudest at lower left sternal border that becomes louder with inspiration. +Right parasternal heave
RESP: CTAB. No expiratory wheezing
ABD: Soft, NT, +distended. Liver edge palpable 3 cm below costal margin
EXT: 2+ bilateral pitting edema of bL LE above the knees, cool distal extremities
NEURO: AAOx3, no gross motor or sensory deficits

Labs:

130 | 95 | 30 /	8.9 \ 12 / 250	ABG: 7.3/36/59/20/89%
---------- 131	/ 36 \	D-dimer = < 0.5
4.5 | 20 | 1.9 \		Lactate = 2.8
		BNP = 1200

CXR: Enlarged pulmonary vasculature, enlarge right cardiac border, clear lung fields
EKG: Sinus tachycardia, right axis deviation, right atrial enlargement, no ST changes

What is the most likely diagnosis? How can you confirm?

Concerning for right heart failure progressing to cardiogenic shock!

- *Sx: worsening SOB, weight gain and swelling*
- *Exam: JVD, LE edema, ascites, hepatomegaly, RV heave, TV regurg murmur, clear lungs!*
- *Labs: hypoNa, elevated Cr (cardiorenal), elevated lactate, elevated BNP*

Could be 2/2 progressive PAH. Though… RH strain increases risk of r-sided MI (RV perfused during diastole & systole, increased wall strain limits blood flow) so could have R-sided MI compounding the problem. She also has hx of hypothyroidism so can consider early myxedema coma

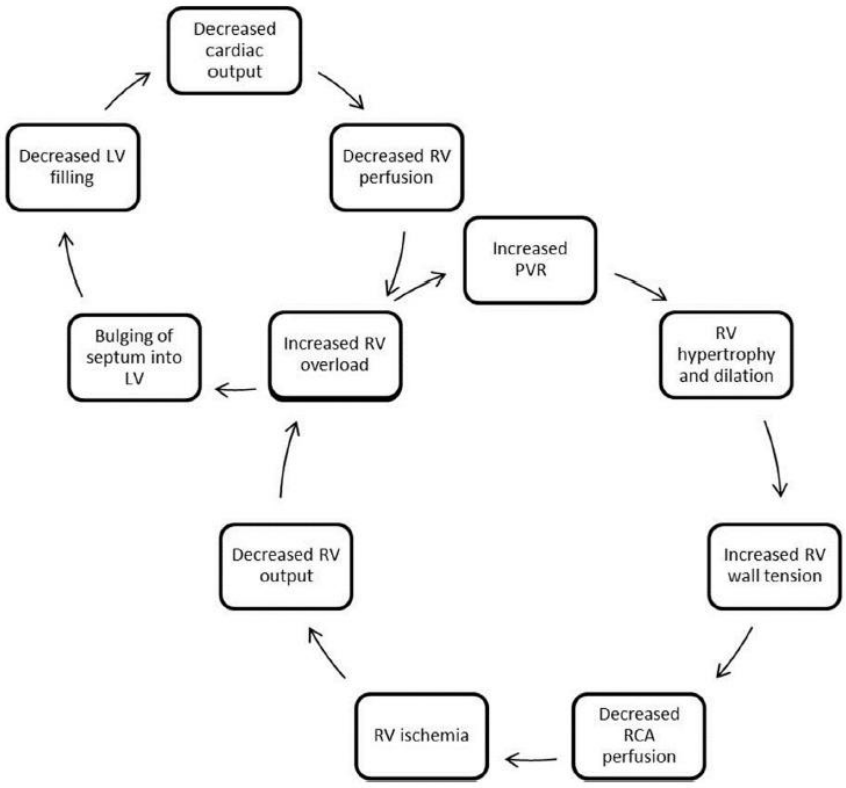
- *If they ask → TSH and troponin are both normal*

RHF is known complication of PAH, leading cause of hospitalization (56% of PAH admissions)

Confirm with bedside and/or formal TTE → Looking for RA and RV dilation, RV hypokinesis, flattening/bowing of septum toward the LV, tricuspid regurgitation

Can you explain the pathophysiology?

Pathophysiology: increased afterload due to progressive PAH → increased RH strain → initial RV hypertrophy → RV dilation → RHF → increased preload → LE edema, ascites → decreased CO → shock (see figure below)



Where do you admit Ms. Lannister? What are your basic treatment goals?

Needs to be admitted to ICU

- *Guidelines recommend ICU for PH patients when HR > 110 bpm, hypotensive (SBP<90), low UOP, rising lactate not explained by other co-morbidities*

Try to break down the treatment options based on the pathophysiology of RHF:

- *Decrease the excessive preload – Diuretics (gentle, avoiding large fluid shifts)*
- *Decrease the elevated afterload – Pulmonary vasodilators*
    - *Increasing therapy from patient's baseline*
    - *Adding IV therapy*
    - *Adding inhaled therapy (epoprostenol, iNO) – theoretically increasing perfusion to ventilated areas*
- *Increase cardiac output: Optimize preload and afterload. Dobutamine is first line ionotrope*