Medication Therapy Review: Pulmonary Hypertension

Purpose: The NPA Medication Management Work Group Clinical Subcommittee recognized pulmonary hypertension as an area of concern for PACE Providers. Pulmonary hypertension has significant morbidity and mortality associated with the diagnosis and requires input from multiple specialists and a full team modality approach to treat. This review provides clinical decision-making assistance with a focus on recommendations for pulmonary artery hypertension.

Definition: Pulmonary hypertension (PH) includes pulmonary artery hypertension (**PAH**) as well as PH caused by left heart disease, chronic lung disease, pulmonary artery obstruction, and PH by unrecognized mechanisms.

Symptoms: Typical symptoms of PH are dyspnea and fatigue, progressing to overt right heart failure (edema, exertional syncope) as it becomes severe.

Incidence: Although PAH was previously felt to be a rare disease and traditionally considered to affect young women, it is known that PAH affects all age groups and both genders, with a female preponderance of 1.8:1 (UptoDate, 2020). The incidence in the elderly is increasing for both PAH and PH. According to PACE Data Analysis Center of the National PACE Association, PH incidence in PACE is about 9.3% as of March 2020. However, PAH is still considered uncommon with incidence estimated at 5-15 cases per one million adults. While survival data is difficult to generalize, older patients have poor outcomes compared to younger patients.

Diagnosis: PH is defined as mean pulmonary arterial pressure >25 mmHg as assessed by right heart catheterization. (Guidelines for echocardiographic diagnosis are included in the UpToDate review entitled: Clinical features and diagnosis of pulmonary hypertension of unclear etiology in adults.)

Classification (ICD-10):

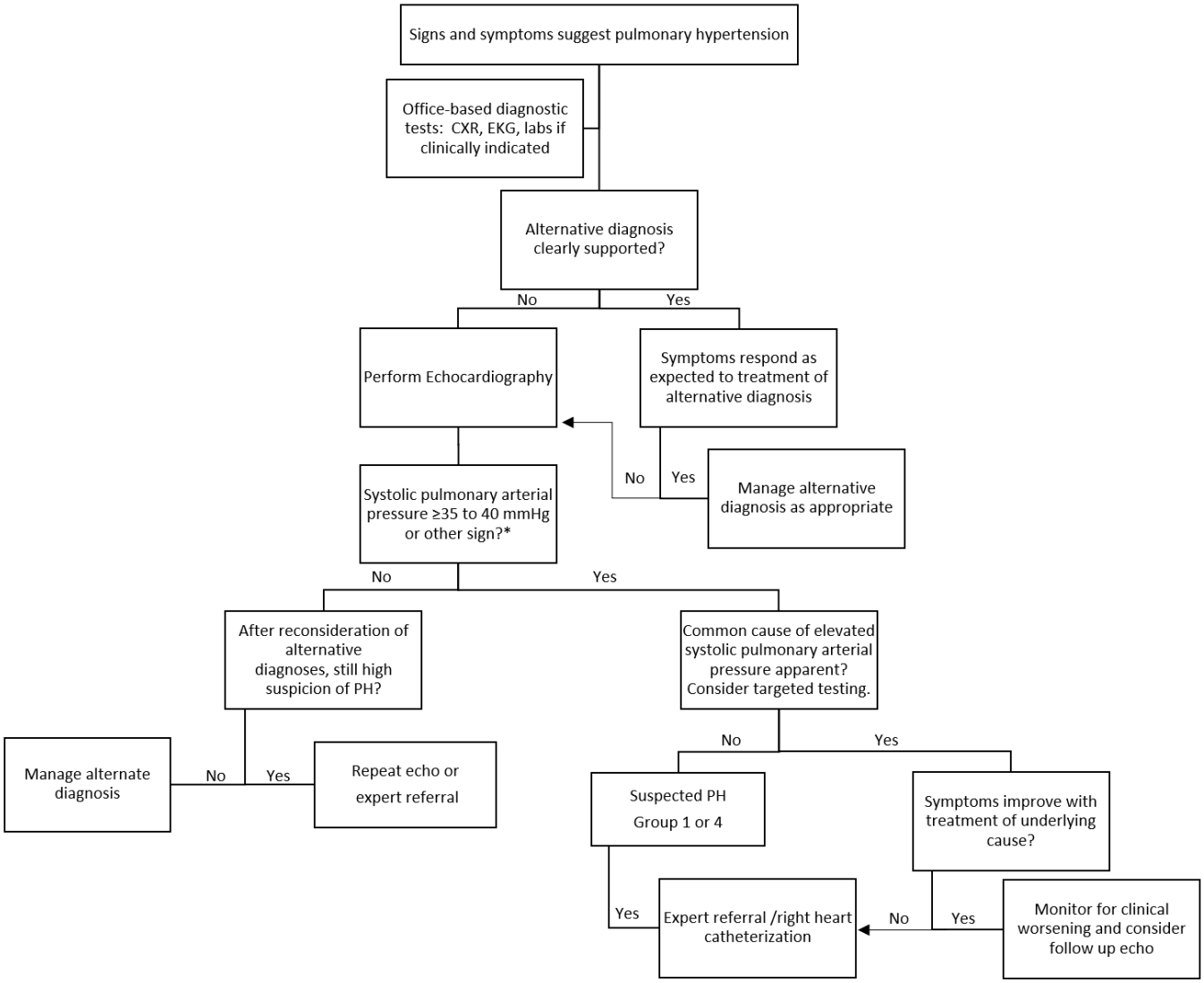
- I27.0 (primary pulmonary hypertension)
- I27.21 (secondary pulmonary arterial hypertension).
- I27.22 (pulmonary hypertension due to left heart disease)
- I27.23 (pulmonary hypertension due to lung disease and hypoxia)
- I27.24 (chronic thromboembolic pulmonary hypertension)
- I27.29 (other secondary pulmonary hypertension)
- I27.20 (unspecified pulmonary hypertension)

Classification (WHO functional classes): Quantify symptoms via history and exercise testing (6-minute walk test) to identify WHO functional class

Class I	Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope.
Class IV	Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity.

Data from: Rich, S. Primary pulmonary hypertension: executive summary. Evian, France. World Health Organization, 1998.

Pulmonary Hypertension Algorithm for Work Up by PACE Primary Care



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Treatment Guidelines

*For the purposes of this review, treatment is focused on Group 1 Primary Pulmonary Hypertension. Group 2-5 treatments should focus on the underlying cause of the disease.

Pulmonary Hypertension Treatment Overview by Groups

Group 1: PAH	Treatment specifically directed at idiopathic PAH • Calcium channel blockers (if they have a positive vasoreactivity test) • Phosphodiesterase 5 inhibitors, plus • Endothelian receptor antagonists
Group 2: PH due to left sided heart disease	Treat underlying heart failure (specific PH treatment may be harmful)
Group 3: PH due to lung disease and/or hypoxia	Treat underlying disease (specific PH treatment may be harmful)

Group 4: PH due to pulmonary artery obstructions	Pulmonary thromboendarterectomy is only cure • Limited evidence suggests use of anticoagulation. Required minimum of 3 months prior to surgery • Consider treatment with riociguat if patient has class IV symptoms and not a surgical candidate
Group 5: PH with unclear and/or multifactorial mechanisms	May consider IV prostacyclin, epoprostenol, or oral bosentan
All Groups	Lifestyle modifications, exercise, and may consider diuretic, oxygen, anticoagulant, and/or digoxin therapy, based on underlying cause

Adapted from UpToDate: Hopkins, W., & Rubin, L. (2019). Treatment of Pulmonary Hypertension in Adults. In J. Mandel (Ed.), *UpToDate.* Accessed June 8, 2019, from https://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults

Pulmonary Hypertension Treatment Overview by Functional Class

Class I: Does not require pharmacologic therapy	• Monitor closely for disease progression • Treat applicable comorbid conditions affecting lung function
Class II and III: Evidence suggests targeting endothelin and nitric oxide-cyclic guanosine monophosphate (cGMP) pathways in combination due to statistically significant reduction in the rate of clinical failure compared to monotherapy	• Initial therapy in drug-naïve: ambrisentan and tadalafil ○ If contraindication to either agent: substitute for another oral endothelin receptor antagonist or PDE5 inhibitor respectively • Alternative: combined oral regimens of two agents from different classes or single agent oral therapy • Class III with rapid progression or other markers of poor clinical prognosis: Prostacyclin agonist
Class IV:	• Parenteral prostacyclin agonist • If parenteral therapy contraindicated or disease progression: Inhaled prostacyclin agonist
Progressive or refractory disease:	• Combination therapy with an agent of a different class and different mechanisms of action • Rarely, a third agent is used

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Pharmacologic Treatment

Treatment for PH may be performed via inhalation, intravenous, subcutaneous, or oral administration

Drug	Route	Cost (AWP)	Pharmacy Availability	Special Considerations & Contraindications
Prostacyclin agonists				
Epoprostenol (Flolan/Veletri)	Continuous IV (Part B)	$4000/month	Limited Distribution: Accredo or CVS Caremark	FDA Indication: PAH (WHO Group 1) with NYHA Class III-IV and PAH associated with scleroderma. Flolan requires refrigeration and cold pouch must be used during infusion to maintain stability.
Iloprost (Ventavis)	Inhaled (Part B)	$3700/month	Limited Distribution; Accredo	FDA Indication: PAH NYHA Class III-IV
Treprostinil (Orenitram/Tyvaso / Remodulin)	Oral Inhaled (Part B) IV/SC (Part B)	$2600/month $2450/month $1300/month (Generic IV similar pricing)	Limited Distribution: Accredo or CVS Caremark	FDA Indication: PAH Oral- NYHA class II-III; Inhaled- NYHA class III; Injection-NYHA class II-IV

Drug	Route	Cost (AWP)	Pharmacy Availability	Special Considerations & Contraindications
Prostacyclin agonists (cont.)				
Selexipaq (Uptravi)	Oral	$17500/month	Accredo or CVS Caremark	FDA Indication: PAH to delay disease progression and reduce the risk of hospitalization
Endothelin receptor antagonists				
Ambrisentan (Letairis)	Oral	$10400/month Generic: $2100/month	Accredo or CVS Caremark	FDA Indication: WHO Group 1 in combination with Tadalafil; (WHO-FC II-III first line; Class IV- Second line) Hazardous agent (NIOSH 2016 [group 3]) REMS Program
Bosentan(Tracleer)	Oral	$5800/month Generic: $3140/month	Accredo or CVS Caremark	FDA Indication: PAH WHO Functional Class II-IV Hazardous agent (NIOSH 2016 [group 3]) Tracleer REMs Program (prescribers, patients, and pharmacies must enroll)
Macitentan (Opsumit)	Oral	$9700/month	Specialty	FDA Indication: PAH Who Group 1 Hazardous agent (NIOSH 2016 [group 3])
Soluble guanylate cyclase stimulants				
Riociguat (Adempas)	Oral	$10400/month	Specialty	FDA Indication: WHO Group 1 and Group 4 Hazardous agent (NIOSH 2016 [group 3]) REMS program Do not use with PDE5 inhibitors or nitrates due to hypotension. Tobacco decreases riociguat levels.
Phoshodiesterase type 5 inhibitors				
Sildenafil (Revatio)	Oral	$4700/month Generic: $100/month	Retail pharmacies, Specialty	FDA Indication: PAH (Primarily WHO/NYHA functional class II and III) Do not use with guanylate cyclase stimulant or nitrates due to hypotension.
Tadalafil (Adcirca)	Oral	$4170/month Generic: $600/month	Retail Pharmacies, Specialty	FDA Indication: PAH (Primarily WHO class II-III) Do not use with guanylate cyclase stimulant or nitrates due to hypotension.
Calcium channel blockers				
Amlodipine	Oral	$235/month Suspension: $600/month Generic: $25/month	Retail pharmacies	Not FDA Approved for PH Titrated every 2 to 4 weeks to clinical effect. Use with caution in liver impairment.
Diltiazem	Oral	$60 to $660/month Generic: $25/month	Retail pharmacies	Not FDA Approved for PH Titrated every 2 to 4 weeks to clinical effect. Use with caution in liver impairment.

Medication Dosing

Drug	Dosing	Side Effects	Monitoring
Prostacyclin agonists: Vasodilation & Antiproliferation			
Epoprostenol (Flolan/Veleteri)	IV: Initial: 2 ng/kg/minute increase ≥15minutes until dose limiting side effect or response Optimal dose (monotherapy): 25 to 40 ng/kg/minute	Flushing, jaw pain, headache, hypotension, nausea	Monitor arterial pressure; assess all vital functions. Hypoxia, flushing, and tachycardia may indicate overdose.
Iloprost (Ventavis)	Initial: inhale 2.5 mcg; If tolerated, increase to 5 mcg administered 6 to 9 times every day during waking hours, no more than once every 2 hours Max daily dose: 45 mcg	Increased cough, flushing, headache, flu-like symptoms	Heart rate, blood pressure, and respiratory rate at baseline and with dosage adjustment
Treprostinil (Orenitram/Tyvaso/ Remodulin)	Initial: 1.25 ng/kg/minute SC or continuous IV infusion; increase dose 1.25 ng/kg/minute per week for the first 4 weeks then by 2.5 ng/kg/minute per week for remaining duration Oral: Initial: 0.25 mg every 12 hours or 0.125 mg every 8 hours Inhaled: Initial: 18 mcg (or 3 inhalations) every 4 hours 4 times/day; Maximum: 54 mcg (or 9 inhalations) 4 times/day	Dizziness, headache, loss of appetite, jaw pain, sepsis, injection site reactions, throat irritation	Blood pressure, dyspnea, fatigue, activity tolerance, symptoms of excessive dose (eg, headache, nausea, vomiting)
Selexipaq (Uptravi)	Initial: 200mcg twice daily Max: 1600 mcg twice daily	Jaw pain, anemia, headache, diarrhea, vomiting	Liver function tests, pulmonary edema
Endothelin receptor agonists: Vasodilation			
Ambrisentan (Letairis)	5mg once daily Maximum: 10mg once daily	Anemia, body fluid retention, headache	Transaminases prior to initiation and monthly during first year, peripheral edema
Bosentan(Tracleer)	<40 kg: Initial and maintenance: 62.5 mg twice daily ≥40 kg: Initial: 62.5 mg twice daily for 4 weeks; increase to maximum maintenance dose of 125 mg twice daily.	Flushing, hypotension, palpitations, lower extremity edema, headache	Serum transaminase (AST and ALT) and bilirubin (prior to treatment initiation and monthly), Hemoglobin and hematocrit (at baseline, at 1 month and 3 months of treatment)
Macitentan (Opsumit)	10 mg once daily; Maximum 10 mg daily	Anemia, headache, UTI, bronchitis, influenza	Liver function tests, peripheral edema, hemoglobin and hematocrit
Soluble guanylate cyclase stimulants: Vasodilation			
Riociguat (Adempas)	Initial: 1mg three times daily Maximum: 2.5mg three times daily	Hypotension, constipation, diarrhea, vomiting	Blood pressure and signs and symptoms of hypotension, peripheral edema

Drug	Dosing	Side Effects	Monitoring
Phoshodiesterase type 5 inhibitors: Vasodilation			
Sildenafil (Revatio)	20mg three times daily (may initiate at lower doses and titrate) Maximum: 80mg three times daily	Hypotension, erythema, flushing, myocardial infarction, nausea, edema, visual impairment	Blood pressure and pulse, pulmonary edema
Tadalafil (Adcirca)	40mg once daily Concurrent use with ritonavir: 20mg once daily	Flushing, headache, backache, indigestion, retinal occlusion/ thrombosis, angina	Blood pressure
Calcium channel blockers: Use in vasoreactive PH only			
Amlodipine	2.5 mg to 40 mg	Edema	Heart rate, blood pressure
Diltiazem	540mg to 900 mg	Peripheral edema	LFT, heart rate, blood pressure

Specialty Pharmacy/Acquisition Information

*Not an all-inclusive list.

Pharmacy	Phone	Fax	Website/Form Link
Accredo Health, Inc	888-200-2811	800-711-3526	https://www.accredo.com/prescribers/referral_forms
CVS Caremark	800-237-2767	800-323-2445	https://www.cvsspecialty.com/wps/portal/specialty/healthcare-professionals/enrollment-forms
Diplomat Pharmacy	877-977-9118	866-410-3762	https://www.diplomatpharmacy.com/condition-resources/pulmonary-arterial-hypertension
Walgreens Specialty	888-782-8443	877-231-8302	https://www.walgreens.com/businesssolutions/provider/referral-forms.jsp?o=acs
Walmart Specialty	877-453-4566	866-537-0877	https://i5.walmartimages.com/dfw/4ff9c6c9-28ca/k2-_a026fb7d-0cab-4a30-a53a-6a01054bc080.v1.pdf

Key Considerations/Questions for Specialists

1. When referring to pulmonology specialist be sure to include description of PACE participant's functional level and one-year mortality risk.
    a. Educate the specialist about PACE services available for treatment and monitoring.
2. Take the following into consideration when managing conversations with specialists:
    a. Is the request in accordance with FDA approved indication?
    b. Does the request follow general medically accepted treatment algorithms?
    c. How does participant comorbidities affect treatment?
    d. Have you discussed with participant the risks/benefits?
    e. Has the specialist been informed of the participant pathway for treatment? i.e. long term care?
3. Key questions to ask specialists:
    a. How should we monitor patient progress?
        i. What are the measurements for success or failure?
    b. What is the diagnosis and functional class?
    c. Was right heart catheterization completed?
        i. If not, treatment is not generally indicated.
    d. What treatments have already been tried?
        i. Reasons for failure?
    e. Secondary pulmonary HTN—is treatment with these drugs necessary or better to focus on primary condition?

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Am Fam Physician. 2016;94(6):463-469. Copyright © 2016 American Academy of Family Physicians.

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