Diagnostic and therapeutic algorithm for pulmonary arterial hypertension

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PULMONARY ARTERIAL HYPERTENSION DIAGNOSTIC ALGORITHM

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) ≥25 mmHg, irrespective of etiology. In contrast to PH, the definition of pulmonary arterial hypertension (PAH) requires the exclusion of elevated pulmonary venous pressure, an established cause of PH, as reflected by a normal wedge pressure or left ventricular end-diastolic pressure (LVEDP) (≤15 mmHg). If PH is suspected in a patient, suitable screening tests are conducted to confirm the presence of PH and delineate the etiology to appropriately tailor an optimal therapeutic regimen. The diagnostic algorithm [Figure 1] reflects an integration of assessment pathways that help differentiate patients with WHO groups II–IV of pulmonary hypertension from WHO group I PAH as well as the subgroups of PAH. Caution is advised to apply the algorithm to any individual patient as the evaluation process of any patient with suspected PH requires a variety of investigations intended to confirm PH and the specific PAH subtype and, once confirmed, evaluate the functional and hemodynamic impairments of those patients. Right heart catheterization is universally considered to be an indispensable part of the diagnostic assessment.

PAH RX ALGORITHM

The treatment algorithm is based on a consensus of the PH community based on the majority of randomized controlled clinical trials (RCTs) for PAH. The grading system is based on the recently published consensus

for these drug trials.[1] Additionally, most trials were conducted in idiopathic or heritable PAH and PAH associated with scleroderma or anorexigen use; hence, the therapeutic effect on other PAH subpopulations may not be equal. Although there are no RCTs to substantiate the use of the following therapies, oral anticoagulation, diuretics in cases of fluid retention and supplemental oxygen in cases of hypoxemia (oxygen saturation <92%) are still considered the first line of treatment in patients with PAH. Acute vasoreactivity testing should be performed in all patients with PAH. Vasoreactivity is defined as reduction of mPAP ≥10 mmHg to reach an mPAP ≤40 mmHg with a normalized or increased cardiac output with acute pulmonary vasodilator challenge (either inhaled nitric oxide, adenosine or intravenous epoprostenol). Vasoreactive patients should be treated with high-dose calcium channel blockers with maintenance of response, defined as WHO functional class I or II with near-normal hemodynamic status, being confirmed by repeat right heart catheterization and clinical assessment after 3–6 months of treatment. Non-responders to acute vasoreactivity testing are defined both hemodynamically as well as by functional class II–IV, and should be considered candidates for other treatments as shown in Figure 2. The choice of the agent is dependent on a variety of factors, including route of administration, side-effect profile, patient preference and the physician's experience and clinical judgment. Continuous IV epoprostenol is the first-line therapy for IPAH and HPAH patients in WHO functional class IV because of its demonstrated survival benefit. Combination therapy should be considered for patients who fail monotherapy.

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Figure 1 (flowchart text):

PH Signs and Symptoms

Non-invasive PH Assessment → No → Re-evaluate at follow-up or with further diagnostic testing if high index of suspicion

Non-invasive PH Assessment → Yes → Contingent Diagnostic Tests: ECG, Chest X-ray, Chest CT, PFT, ABG, TTE/TEE, Stress test, Polysomnography, LH catheterization (at time of RHC), V/Q scan

WHO Group II-IV PH Confirmed → Yes → Treat underlying cause with close follow-up for progression

No or PH out of proportion to underlying diagnosis

Evaluate for Other Causes

RHC and Vasodilator Testing → No → Evaluate for Other Causes

RHC and Vasodilator Testing → Yes (resting mPAP >25 mmHg and LVEDP ≤15 mmHg)

Diagnostic WHO Group I PAH testing:
ANA for CTD
HRCT for CTD/PVOD/PCH/PE
Toxin/Drugs
Shunt run/CMR/Cardiac CT for CHD
LFTs/US for portopulmonary hypertension
Lab testing for hemlytic anemia-associated, other PAH causes

→ Positive Treat as indicated

→ Negative → Evaluate FMHx and consider genetic testing for BMPR2/ALK2/endoglin (HHT)

No → Idiopathic pulmonary arterial hypertension

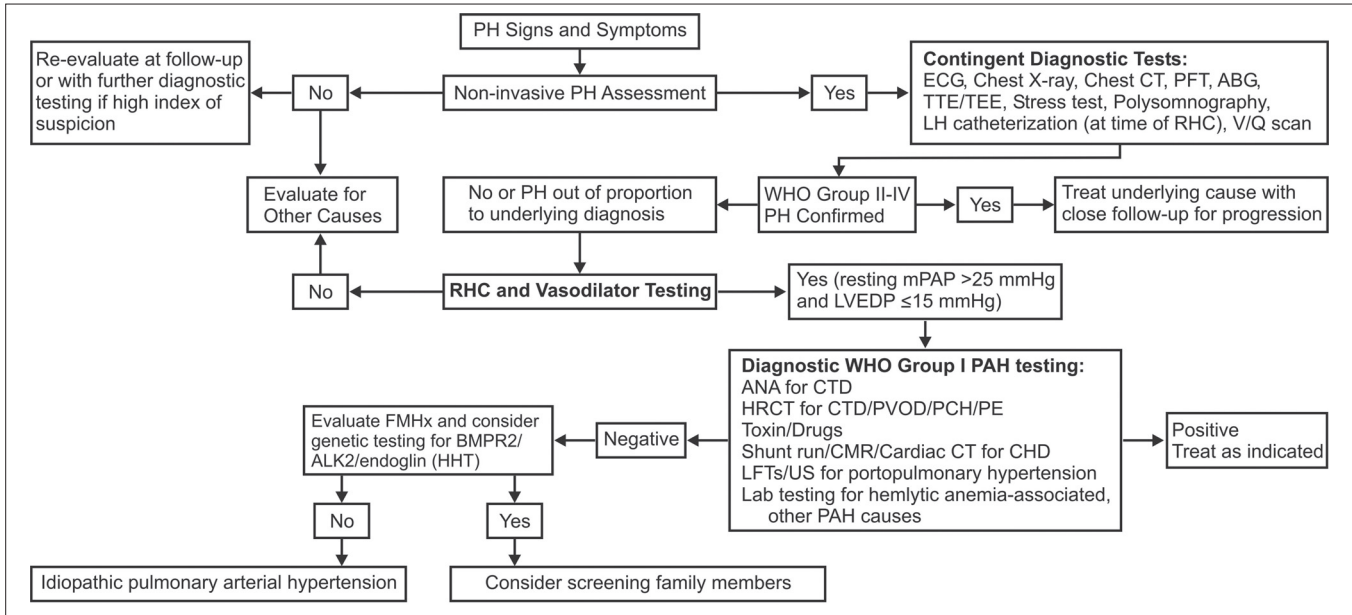Yes → Consider screening family members

Figure 1: PAH diagnostic algorithm. (ABG - Arterial blood gas; ALK-1 - Activin-receptor-like kinase; ANA - Anti-nuclear antibodies; BMPR2 - Bone morphogenetic protein receptor 2; CHD - Congenital heart disease; CMR - Cardiac magnetic resonance; CT - Computed tomography; CTD - Connective tissue disease; ECG - Electrocardiogram; FMHx - Family medical history; HHT - Hereditary hemorrhagic telangiectasia; HRCT - High-resolution computed tomography; LFTs - Liver function tests; LH - Left heart; PAP - Pulmonary arterial pressure; LVEDP - Left ventricular end-diastolic pressure; PAH - Pulmonary arterial hypertension; IPAH - Idiopathic pulmonary arterial hypertension; PCH - Pulmonary capillary hemangiomatosis; PE - Pulmonary thromboembolic disease; PFT - Pulmonary function test; PH - Pulmonary hypertension; PVOD - Pulmonary veno-occlusive disease; RHC - Right heart catheterization; TEE - Transesophageal echocardiography; TTE - Transthoracic echocardiography; US - Ultrasonography; V/Q - Ventilation/perfusion lung scan; WHO - World Health Organization)

Figure 2 (flowchart text):

Advise all PAH patients
Avoid excessive physical exertion, birth control, infection prevention
Consider supervised rehabilitation and psychological and social support, oxygen therapy
Expert referral → Acute vasoreactivity test
Yes, with sustained response → Treat with high-dose Ca²⁺ channel blockers (amlodipine, diltiazem, nifedipine)²⁻⁷
Non-responder → Refer to Table → Inadequate response → Atrial septostomy or lung transplantation

Medication	Trade Name	Class	Route	FC-II	FC-III	FC-IV	References
Digoxin	Lanoxin		PO/IV	E/C	E/C	E/C	8
Diuretics			PO/IV	E/A	E/A	E/A	No study
Warfarin	Coumadin		PO	E/B	E/B	E/B	2, 9-11
Bosentan	Tracleer	ERA	PO	A	A	E/C	12-17
Ambrisentan	Latairis	ERA	PO	A	A	E/C	18-20
Sildenafil	Revatio	PDE-I	PO	A	A	E/C	21
Tadalafil	Adcirca	PDE-I	PO	B	B	E/C	16
Beraprost	Procylin	Prostanoid	PO		NA(C)	NA	22-23
Iloprost	Ventavis	Prostanoid	Inhaled		A	B	24
Treprostinil	Tyvaso	Prostanoid	Inhaled		NA	NA	25
Iloprost	Ilomedine	Prostanoid	IV		E/B	E/B	26
Epoprostenol	Flolan	Prostanoid	IV		A	A	27-28
Treprostinil	Remodulin	Prostanoid	IV		E/B	E/B	29-30
Treprostinil	Remodulin	Prostanoid	SC		B	C	31-32
Sequential Combination Therapy (for inadequate monotherapy response)							
Prostanoid+PDE-I		Combination	IV/PO or Inhaled			B	33-34
Prostanoid+ERA		Combination	IV/PO			B	33, 35-37
ERA+PDE-I		Combination	PO/PO			B	16
Prostanoid+PDE-I or ERA		Combination	Inhaled/PO		B	B	38

Figure 2: PAH treatment algorithm. (PAH - Pulmonary arterial hypertension; FC - Functional class; ERA - Endothelin receptor antagonist; PDE-I - Phosphodiesterase type 5 inhibitor; IV - Intravenous; PO - Oral; SC - Subcutaneous; NA - Not approved; WHO - World Health Organization; PAP - Pulmonary arterial pressure; RCT - Randomized controlled trial. Strength of recommendation: A - Strong recommendation; B - Moderate recommendation; C - Weak recommendation; D - Negative recommendation; E/A - Strong recommendation on the basis of expert opinion only; E/B - Moderate recommendation on the basis of expert opinion only; E/C - Weak recommendation on the basis of expert opinion only; E/D - Negative recommendation on the basis of expert opinion only)

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