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Pulmonary Hypertension

About the Guideline

- Members of the task force were selected by the ESC (European Society of Cardiology) and ERS (European Respiratory Society) to represent professionals who are involved with the medical care of patients with pulmonary hypertension (PH), along with a patient delegate to create a unified guideline.
- The task force evaluated large selections of published guidelines for the diagnosis and treatment of PH.
- The resulting guideline is a comprehensive review of literature from published evidence for the management, diagnosis, treatment, prevention, and rehabilitation of PH.

Key Clinical Considerations

PH is a pathophysiological disorder that can involve multiple clinical conditions and highly complicate those conditions of the respiratory and cardiac systems. It requires a multidisciplinary approach to treatment.

Hemodynamic definitions of PH

Right heart catheterization is the method used to obtain hemodynamic values classifying PH. A complete diagnosis of PH is made by combining hemodynamics along with clinical findings.

- PH: mean pulmonary arterial pressure (mPAP) greater than 20 mm Hg
- Pre-capillary PH, in the absence of other causes: mPAP equal or greater than 20 mm Hg; pulmonary artery wedge pressure (PAWP) equal or greater than 15 mm Hg; pulmonary vascular resistance (PVR) greater than 2 wood units (WU)
- Isolated postcapillary PH: mPAP greater than 20 mm Hg; PAWP greater than 15 mm Hg and/or PVR less than or equal to 2 WU
- Combined pre- and postcapillary PH: mPAP greater than 20 mm Hg; PAWP greater than 15 mm Hg and/or PVR greater than 2 WU
- Exercise PH: mPAP/CO slope amid rest and exercise greater than 3 mm Hg/L/min

Clinical classifications

Group 1 - Pulmonary arterial hypertension (PAH)

- idiopathic; includes both those patients who do not respond and those who respond acutely to vasoreactivity testing; heritable; drug and toxin induced; associated with connective tissue disease, human immunodeficiency virus [HIV] infection, portal hypertension, congenital heart disease, and schistosomiasis; PAH with features of venous/capillary contribution; continuous PH in the newborn.

Group 2 - PH due to left heart disease

- heart failure with well-maintained ejection fraction; heart failure with diminished or mildly diminished ejection fraction; valvular heart disease; postcapillary PH caused by congenital/acquired cardiovascular disorders.

Group 3 - PH due to lung diseases and/or hypoxemia

- obstructive pulmonary disease or emphysema; restrictive lung disease; other pulmonary diseases with mixed restrictive and obstructive pattern; hypoventilation disorder; hypoxia without pulmonary illness (such as high-altitude); and developmental lung diseases.

Group 4 - PH related to pulmonary artery obstructions

- chronic thromboembolic PH; other pulmonary artery obstructions.

Group 5 - PH with unclear or multifactorial mechanisms

- hematologic disorders; systemic disorders; metabolic disorders; chronic renal failure with or without dialysis; pulmonary tumor thrombotic microangiopathy; and fibrosing mediastinitis.

Diagnosis

- A diagnosis of PH starts with suspicions based on clinical symptoms such as progressive right ventricular (RV) dysfunction, shortness of breath (a primary symptom with minimal exertion), angina, weakness, fatigue, and syncope. In some cases, symptoms can also include dry cough, exercise-induced nausea and vomiting, and symptoms that occur at rest (in advanced stages).
- Other physical symptoms that might be present include the following: hemoptysis related to rupture of hypertrophied bronchial arteries, hoarseness, wheezing, and significant dilation of the pulmonary artery (PA). Dilation of the PA may result in rupture, leading to signs and symptoms of cardiac tamponade, a RV third heart sound, pansystolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary regurgitation, increased jugular venous pressure, hepatomegaly, ascites, peripheral edema and cool extremities, and other symptoms related to possible underlying causes of the disease.

Testing

- Electrocardiogram (ECG): abnormalities may include P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block, and QTc prolongation. Prolongation of the QRS complex and QTc suggest severe disease.
- Chest radiography: abnormalities may include central pulmonary arterial dilatation and signs suggesting lung disease or pulmonary venous congestion due to left heart disease.
- Pulmonary function tests and arterial blood gases: test results would indicate mild to moderate reduction of lung volumes, decreased lung diffusion capacity for carbon monoxide, peripheral airway obstruction, and normal or decreased PaO_2 with decreased $PaCO_2$.
- Echocardiography: used to image the effects of PH on the heart and may be used to assign a level of probability to a PH diagnosis; result can determine the need for cardiac catheterization in individual patients. The probability of PH can be classified by the following parameters:
    - *Low probability:* peak tricuspid regurgitation velocity less than or equal to 2.8 m/s, or not measurable and without the presence of other echocardiographic signs of PH
    - *Intermediate probability:* either peak tricuspid regurgitation velocity less than or equal to 2.8 m/s, or not measurable and with the presence of other echocardiographic signs of PH; or peak tricuspid regurgitation velocity of 2.9 to 3.4 m/s without the presence of other echocardiographic signs of PH
    - *High probability:* either peak tricuspid regurgitation velocity of 2.9 to 3.4 m/s with the presence of other echocardiographic signs of PH; or peak tricuspid regurgitation velocity greater than 3.4 m/s regardless of the presence of other echocardiographic signs of PH

- Ventilation/perfusion (V/Q) lung scan: performed to look for chronic thromboembolic PH (CTEPH). Results may be normal or may show small peripheral unmatched and non-segmental defects in perfusion.
- Non-contrast and contrast-enhanced chest computed tomography (CT) and digital subtraction angiography (DSA):
    - CT of the chest may raise suspicion of PH by showing an increased PA diameter (greater than or equal to 30 mm) and a PA-to-aorta ratio greater than 0.9, with right heart chambers that are increased in size; or the following 3 parameters combined: PA diameter greater than or equal to 30 mm, right ventricular outflow tract wall thickness greater than or equal to 6 mm, and septal deviation greater than or equal to 140° or RV:LV ratio greater than or equal to 1.
    - CT pulmonary angiography: can delineate signs of CTEPH, bands and webs, and filling defects.
    - DSA is a confirmatory diagnostic tool for CTEPH and assists in choices for treatment.
- Cardiac magnetic resonance imaging (MRI): can provide an assessment of atrial and ventricular size, morphology, and function, as well as a noninvasive assessment of blood flow in the PA, aorta and vena cava assessing stroke volume, retrograde flow and intracardiac shunt
- Blood tests to include chemistry, hematology, immunology, HIV testing, and thyroid function tests: blood tests are useful only in checking for organ damage related to PH and for underlying causes of PH
- Abdominal ultrasound: can be useful for identification of some of the diseases associated with the causes of PAH
- Cardiopulmonary exercise testing (CPET): low end tidal partial pressure of carbon dioxide ($PETCO_2$), high ventilatory equivalent for carbon dioxide (VE/CO_2), low oxygen pulse (VO_2/HR), and low peak oxygen uptake (VO_2) are common findings with PAH.
- Right heart catheterization and vasoreactivity exercise and fluid challenge: required to confirm the diagnosis of PAH and CTEPH, to assess the severity of hemodynamic impairment, and to undertake vasoreactivity testing for those being considered for treatment with high-dose calcium channel blockers (CCB); right heart catheterization exercise is important to avoid misclassification of patients with an elevated PAWP; the information the hemodynamic response provides with PAH to a fluid challenge is inadequate to provide recommendations.
- Genetic testing: used for those with hereditary and familial relations to PAH.

Treatment

- Overall treatment goals: achievement of low-risk status, good quality of life, good exercise capacity, good RV function, and low mortality risk.
- Treatment includes a complex strategy, not just prescription drug therapy; the drug therapy effectiveness has not been proven in PAH patients with mPAP less than 25 mm Hg and PVR less than 3 WU.
    - General measures:
        - Physical activity and supervised rehabilitation
        - Anticoagulation
        - Diuretics

    - O_2 therapy
    - Cardiovascular medications
    - Anemia and iron status
    - Vaccination
    - Psychosocial support
    - Adherence to treatments
- Special circumstances:
    - Pregnancy
    - Contraception
    - Surgical procedures
    - Travel and altitude

PAH therapy

- Initial therapy with high-dose CCBs in vasoreactive patients, or drugs approved for PAH in nonvasoreactive patients, according to their established prognostic risk.
- In cases where the patient has an inadequate response, the role of combination drug therapy or lung transplantation are proposed.
- Medications used in treatment of PH are as follows:
    - Diuretics for patients with symptoms of RV failure and fluid retention
    - Continuous long-term oxygen therapy for patients with arterial blood O_2 pressure that is consistently less than 8 kPa (60 mmHg or O_2 saturation less than 92%)
    - Oral anticoagulant therapy for patients with idiopathic PAH (IPAH) may increase survival; however, the data available is not substantial enough to make a recommendation in favor of or against anticoagulation and should be determined on a case by case basis.
    - Angiotensin-converting enzyme inhibitors, angiotension-2 receptor antagonists, beta-blockers, and ivabradine should be used only for PAH patients who require them to treat comorbidities.
    - Iron and other anemia correction therapy
    - Endothelin receptor antagonists (ambrisentan, bosentan, and macitentan) for decreasing activation of the endothelin system in both plasma and lung tissues
    - Phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators (sildenafil, tadalafil, and riociguat) cause significant pulmonary vasodilation.
    - Prostacyclin analogs and prostacyclin receptor agonists (beraprost, epoprostenol, iloprost, trepostinil, and selexipeg), which induce potent vasodilation of all vascular beds, are endogenous inhibitors of platelet aggregation and appear to have both cytoprotective and antiproliferative activities.
    - Experimental compounds and strategies: treatment can include other medications targeted at diverse pathobiological changes that are being explored.
    - Combination therapy is often used and employs two or more different medication classes in treatment.

Drug interactions

- Bosentan may reduce the effectiveness of sildenafil and hormonal contraceptives when used in combination. If bosentan is used with a Vitamin K antagonist (VKA), changes may need to be made to the VKA dose.

Interventional therapy

- Balloon atrial septostomy and Potts shunt
    - This procedure is not performed often with PAH patients due to the increased risk of mortality; the purpose is to help decompress the right heart chambers and increase systemic blood flow for better oxygenation.
- PA denervation
    - Remains an experimental modality at this time.

Advanced RV failure

Intensive care unit management

- Patients with PAH who require ICU treatment should be managed in specialized centers whenever possible.
- Basic monitoring to be performed includes vital signs, urine production, central venous pressure, central venous O_2 saturation, blood lactate levels, biomarkers such as NT-proBNP and troponin, and noninvasive echocardiography.
- Low central venous O_2 saturation, rising lactate levels, and low or absent urine production can signify imminent right heart failure.
- Treatment and management of triggering factors is important to prevent total RV failure:
    - Anemia
    - Arrhythmias
    - Infections
    - Optimizing fluid balance
    - Reduction of RV preload
    - Improvement of cardiac output
    - Maintaining systemic blood pressure above 60 mm Hg
- Intubation should be avoided, if possible, as it can result in hemodynamic collapse.

Mechanical circulatory support

- Extracorporeal membrane oxygenation (ECMO) should be considered for some patients.
    - Can be used as a bridge to recovery or transplant in these patients.
    - Should be done only at a highly specialized center, therefore consideration should be given to interhospital transfer when such resources are otherwise unavailable.

Lung and heart-lung transplantation

- Referral to evaluate for possible lung transplantation should occur when a patient is considered at intermediate-high or high risk or has a REVEAL risk score of 7 or more.
- The patient should be placed on the transplant list if at high risk for mortality despite optimized medical care, or if the patient has a REVEAL risk score of 10 or more.

- Bilateral lung transplant alone is more commonly performed unless the patient presents with a cardiac condition that is not fixable; then, a lung-heart transplant is considered.

Diagnosis and treatment of PAH complications

Arrhythmias

- Supraventricular arrhythmias such as atrial flutter and atrial fibrillation are the most common arrhythmias seen in PAH patients and should be treated as soon as possible. They can lead to clinical deterioration with a higher mortality risk.

Hemoptysis

- Hemoptysis is a recognized complication of PH and represents a risk factor for mortality.
- Can range from mild to very severe and lead to death.
- PAH patients should undergo a CT scan with contrast with an arterial phase to evaluate potential bleeding from enlarged bronchial arteries.
- Bronchial artery embolization procedure should be performed for cases of moderate to severe hemoptysis and those with repeated mild cases of hemoptysis.

Mechanical complications

- Mechanical complications are related to progressive dilation of the PA and can include the following:
    - PA aneurysms, rupture and dissection, and compression of nearby anatomy such as left main coronary artery, main bronchi, pulmonary veins, and recurrent laryngeal nerves.
    - Such complications are often determined by an incidental finding as patients are often asymptomatic and symptomatology can be vague.

End-of-life care and ethical issues

- Patients with PH may die slowly, or suddenly, making life expectancy difficult to estimate.
- Open and sensitive communication needs to be used to allow patients to plan in advance, discuss fears, and convey concerns and wishes.
- The patient should be made aware that CPR in severe PH has a poor outcome.
- Arrangements should be made for end-of-life care, if the patient wishes.
- End-of-life care should be done with a multidisciplinary team and should focus on controlling distressing symptoms and discontinuing unnecessary medication.
- This care should also include psychological, social, and spiritual support.
- Palliative care may need to be consulted.

Reference:

Humbert, M., Kovacs, G., Hoeper, M. M., Badagliacca, R., Berger, R. M. F., Brida, M., Carlsen, J., Coats, A. J. S., Escribano-Subias, P., Ferrari, P., Ferreira, D. S., Ghofrani, H. A., Giannakoulas, G., Kiely, D. G., Mayer, E., Meszaros, G., Nagavci, B., Olsson, K. M., Pepke-Zaba, J., Quint, J. K., … ESC/ERS Scientific Document Group (2022). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European heart journal, 43*(38), 3618–3731. https://doi.org/10.1093/eurheartj/ehac237