



DIAGNOSING AND TREATING PULMONARY HYPERTENSION

Understanding the professional guidelines



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Introduction

Who is this document for and what is it about?

This document explains the recommendations in the joint European Society of Cardiology (ESC) and European Respiratory Society (ERS) clinical guidelines for pulmonary hypertension (PH). It is for people with PH, or their family or carers.

This guideline has updated a previous version of ESC/ERS PH guidelines produced in 2015. It includes new developments in the field, including treatments and more knowledge of how PH affects the body and what could cause it.

What are clinical guidelines?

Clinical guidelines are produced after a scientific process used to gather the latest evidence on a condition or symptom. Guidelines also take into account the opinions of experts and the priorities of patients and carers who have experience of a condition. Clinical guidelines are written for healthcare professionals. They use them as a best practice document on how to diagnose, manage and treat a condition.

What does this document include?

This document summarises the key points from the clinical guidelines on PH. It explains them in a way that is easier to understand for people who do not work in a medical field. It will explain what PH is and recommendations to diagnose and treat it.

It outlines the areas covered on the topic and specific recommendations from the guideline. These are divided into:

- ✔ **Strong recommendations**, where there is good evidence and/or general agreement from the authors of the guideline
- ❓ **Ideas to consider**, where there is conflicting evidence or a difference in opinion from the authors of the guideline
- ⊗ **Recommendation against**, where there is good evidence and/or agreement against a particular treatment or approach.

By providing this information in an accessible way, this document aims to help people with PH to understand more about the condition and how it will be managed. This can help someone feel informed when making decisions about their treatment options.

What is pulmonary hypertension?

PH is caused by high blood pressure in the blood vessels called the pulmonary arteries. They are responsible for carrying blood from the heart to the lungs. The arteries become thick or blocked and blood cannot flow through as well.

The condition can damage the right part of the heart which pumps blood to the pulmonary arteries. It can lead to right-sided heart failure and can be fatal. PH can occur on its own but it is more common in people who have another heart or lung condition. This makes the diagnosis and treatment complicated. It often requires input from professionals in different areas of medicine – for example, experts in lung health, heart health, radiology and thoracic surgery.



Diagnosing pulmonary hypertension

Symptoms of PH may develop slowly. They usually get worse as the disease progresses. They include shortness of breath when doing activities or when bending forwards, tiredness, heart palpitations (when your heartbeat feels unusual or uncomfortable) or swelling or weight gain from holding more water in the body.

If your doctor suspects that you have PH, they will look at your symptoms and how you are feeling. There are two main goals at this stage:

- To make sure that anyone who is thought to have a severe form of PH is referred to a specialist treatment centre as soon as possible.
- To check for other underlying conditions, such as lung or heart conditions. This will help to find out the kind of PH you have to ensure you receive the right treatment.

Tests

There are a range of tests that can be used to diagnose PH. After looking at your symptoms and how you are feeling, your doctor will refer you for further tests if they think you may have PH.

There is a precise process they will follow to help determine this. Each test aims to confirm PH and pinpoint what kind of PH you may have and how severe it is.

Two main tests:

Echocardiography

This test uses ultrasound to build up a moving picture of your heart using sound waves. This is similar to the test used during pregnancy to hear a baby's heartbeat. The guideline recommends this as the first test to check for PH. It is non-invasive, meaning that it is a procedure that does not break the skin or remove tissue from the body.

Right heart catheterisation

This is the best available test for PH. This is an invasive procedure – meaning it does involve breaking the skin. It involves inserting a small, bendy tube into a vein in your body. This is fed through to the arteries to measure the blood pressure in the right side of your heart and pulmonary arteries. This allows for an accurate diagnosis of PH. You are usually awake during the procedure but the area of your body where the tube is inserted will be numbed. This test is carried out by trained professionals in specialist PH centres.

- ✓ Right heart catheterisation is recommended to confirm a diagnosis of PH. This test should take place in experienced centres and follow standard procedures.

Other tests could include:

Imaging tests (scans)

Scans of the lungs are recommended to search for the cause of PH. This could be a CT scan, where x-ray and computers are used to create detailed images of the lungs. Or it could be a perfusion lung scan. This is when dye is fed through a tube into the body. It can then be traced by a scanner as it moves around the body. It will gather at areas where blood is not moving around properly in the lungs, which may show there is a blockage.

Lung function tests

This test includes blowing as hard and as fast as you can into a device called a spirometer. This measures how well your lungs are working. It is recommended that your doctor gives you a lung function test when they first suspect PH.

Blood tests

Routine blood tests should be used to find any underlying conditions that are linked to PH.

Exercise tests

These tests usually involve doing some mild exercise, such as walking for six minutes in a corridor. Before, during and after the test, measurements, such as your heart rate, blood pressure and oxygen levels, are taken. Alternatively, a more in-depth test can be performed while exercising on a treadmill or a bike: before, during and after the activity, you will be asked to breathe through a mouthpiece and have your heartbeat monitored. This will help doctors understand how your heart and lungs are working during activity.

Vasoreactivity test

This test is recommended for some people who have received a diagnosis of PH. It takes place during the right heart catheterisation test described above. A test drug is given through a tube or by breathing it in to see how well your body responds to it.

- ✔ This test is recommended for certain groups of people with pulmonary arterial hypertension (PAH), but not everyone. It looks at whether you might benefit from using a kind of medicine called calcium channel blockers. The test should be performed at a specialist PH centre.

Confirming a diagnosis

The guideline recommends the following process to diagnose PH:

- ✔ A review of the symptoms a person describes, observations taken by a doctor and a range of test results can be used to diagnose PH.
- ✔ Genetic tests that reveal a specific error in a person's DNA (known as a genetic mutation) can confirm whether PAH can be passed from a parent to a child.
- ✘ Lung biopsy is not recommended to confirm a diagnosis of PH.

Types of pulmonary hypertension

PH includes many different types of the disease. PH can be categorised into five groups, based on different causes.

Group 1: Pulmonary arterial hypertension (PAH)

PAH is caused by high pressure in the blood vessels that carry blood from the heart to the lungs. This happens due to changes in the structure of the pulmonary arteries which are thick or blocked.

Subsets of PAH

PAH may be linked to your genes (labeled as heritable PAH), induced by drugs or toxins, or associated with other diseases (such as liver disease, autoimmune disease such as scleroderma, congenital heart disease, human immunodeficiency virus (HIV) infection and schistosomiasis, caused by a parasitic worm that lives in fresh water in subtropical and tropical regions). When no cause is identified, PAH is labeled as idiopathic.

Classifying the impact of PAH

When you are diagnosed with PAH, your doctor will look at how the disease is affecting physical activities. It will be grouped as one of four types:

- Ordinary physical activity does not cause you any symptoms (functional class I)
- You are comfortable when resting but ordinary physical activity such as climbing 1-2 flights of stairs could cause shortness of breath, or chest pain (functional class II)

- Slightly raised activity levels, such as climbing just 1 flight of stairs can cause symptoms and make you stop in between but you are comfortable resting (functional class III)
- Shortness of breath and tiredness may be there when resting and any physical activity causes you discomfort (functional class IV)
- ✓ PAH should be grouped based on the results from a range of tests taken and examination by a doctor.

Monitoring PAH

A physical check-up at the doctors is a key part of monitoring PAH. It helps to provide valuable information on how severe the disease is, whether it has got better or worse, or whether it has stayed the same. You will also receive ongoing tests, such as blood tests or exercise capacity tests to check how your disease is progressing. Questionnaires can also be used to look at how the disease is having an impact on your quality of life.

Treatment for PAH

- ✓ Treatment plans should aim to lower the risk of the disease for each individual.

A full treatment plan will be given that will include medication and lifestyle changes. This will be put together through shared decision making between you and your healthcare professional. General treatments and lifestyle changes could include:

- ✓ Physical activity or rehabilitation at a level that is suitable for you.



- ✓ Seeking support for any mental health issues and accessing support from patient support groups.
- ✓ Keeping up to date with your vaccinations such as flu and COVID-19.
- ✓ Diuretic medicine if needed, which encourages more urine production. This is taken as a tablet and helps your body get rid of excess water it is holding.
- ✓ Oxygen therapy if needed, which improves oxygen delivery in your body.
- ✓ Iron supplements if needed, which can help people who do not have enough iron in their blood.
- ✗ Anticoagulation medicine, which reduces the risk of blood clots. This is not usually recommended for people with PAH but might be considered on an individual basis.

PAH medication could include:

- **Calcium channel blockers** – this is a group of medicines that helps to open up the pulmonary blood vessels. The main drugs that are used for PAH are nifedipine, diltiazem and amlodipine. They are taken as a tablet. They are not suitable for all people with PAH. The vasoreactivity test is able to determine whether this drug is right for you or not. Once you are taking this medicine, you should be assessed every 3-6 months to see how you are responding to this treatment.
- **Endothelin receptor antagonists** - this medication works by reducing the effect of a substance in the blood called endothelin. People with PH produce too much endothelin,

which can cause the blood vessels to become narrower. The main drugs used for PAH are ambrisentan, bosentan and macitentan. These are taken as a tablet. Some medicines such as bosentan can have an effect on the liver and people on this medication should have regular liver function tests to check for any side effects. Endothelin receptor antagonists should not be used in pregnancy.

- **Phosphodiesterase 5 inhibitors and guanylate cyclase stimulators** – this medication works by helping the pulmonary blood vessels to relax, which can help increase blood flow and lower blood pressure. The main drugs used for PAH are sildenafil, tadalafil and riociguat. These are taken as a tablet.
- **Prostacyclin analogues and prostacyclin receptor agonists** – this group of medicines also work by opening up the pulmonary blood vessels to allow more blood flow. The main drugs used for PAH are epoprostenol, iloprost, treprostinil, beraprost and selexipag. Depending on the medications used, these are taken as a tablet, by inhalation, or through a pump delivering the drug either under the skin (subcutaneous) or in a vein (intravenous). Oral treprostinil and beraprost are not currently approved for use in all European countries.

Treatment plans are different for the different types of PAH and for each individual. As treatments target different elements of your condition, they will sometimes be used on their own or more commonly combined with other medication. Your specialist will discuss which medications and lifestyle changes will be best for you and form a plan to follow. This will be monitored and adjusted depending on how well you are feeling.

Intensive care treatment

If you experience right heart failure, you will require treatment in an intensive care unit.

- ✔ It is recommended that you receive support to treat the cause of heart failure and help your symptoms. This could include medication and fluid management. A machine that helps your heart to pump blood could also be used in some circumstances, usually as a bridge to lung transplantation – this is known as mechanical circulatory support or extracorporeal membrane oxygenation (ECMO). If this is not available at your hospital, your healthcare team may consider moving you to another centre.

Lung and heart-lung transplantation

- ✔ You may be referred for a lung or heart-lung transplant in some circumstances. Referral should happen if you do not improve with the medication you have been given or if you have very severe disease that could be fatal.

Palliative and end-of-life care

When you are first diagnosed with PAH, you will learn about how severe your disease is and what your prognosis is – the likely course your disease will take. Life expectancy is difficult to predict as PAH can progress either slowly over a number of years or very quickly leading to sudden worsening or death.

People who are approaching the end of their life will require regular checks by professionals from different areas of medicine to look at what support they need. Open communication between you and your healthcare professional will allow you to discuss any fears, concerns and wishes you have. It will also help you to make a joint decision about your treatment options and care at the end of your life.

Other factors to consider

Pregnancy and contraception

Women with PAH are more at risk of complications during pregnancy and birth. In some cases, going through pregnancy and birth can make your disease worse.

- ✓ Healthcare professionals should discuss pregnancy with women of childbearing age when they are diagnosed with PAH. In women with PAH, becoming pregnant is associated with several risks. If you are considering pregnancy you should be fully informed of the risks and discuss them with your specialist. The decision can be taken after looking at how well controlled symptoms are, what stage the disease is at and the individual risk of complications.

- ✓ This can be a very distressing time for some people and if you need further support, referrals to psychological services should be given.
- ✓ If you become pregnant, or if you decide to terminate a pregnancy, you should be treated and monitored closely at a specialist PH centre.
- ✓ Some forms of contraception can also be affected by your disease or the medication you are taking. Your healthcare professional should discuss which is best for you.

Surgery

- ✓ There is an increased risk of complications with surgery and general anaesthetics if you have PAH. Decisions about whether to undergo any surgical procedures should be discussed with your specialist.

Travel and altitude

Air travel can have a harmful effect on symptoms. Evidence suggests that most people who have stable symptoms will be able to travel by air without an issue if the journey is less than 24 hours. The guideline advises people to avoid spending long periods of time at high altitude (more than 1500m) without any oxygen supplements.

- ✓ If you are already using oxygen then you would need to take this on a flight with you.
- ✓ Whenever you travel, it is recommended that you keep written information about your disease and medication with you. It is also useful to find specialist PH centres in the area you are travelling to in case they are needed.

Specific subsets of PAH

There are some specific forms of PAH that require different approaches and treatment plans. These are outlined below:

Pulmonary arterial hypertension associated with drugs or toxins

In some cases, drugs and toxins have been found to cause PAH. Drugs that suppress your appetite, methamphetamines (a drug that is illegally used for enjoyment), interferons (which are sometimes used to treat viral infections) and some cancer drugs have all been linked with PAH.

- ✓ Healthcare professionals should diagnose drug- or toxin-associated PAH in people who have been exposed to these drugs or toxins when other causes of the condition have been ruled out. Exposure to the drug or toxin should be stopped immediately. People at high risk should start PAH treatment straight away. People at low risk should be monitored every few months to see if it is needed.

Pulmonary arterial hypertension associated with connective tissue disease

PAH can be a complication of different connective tissue diseases. These are diseases that affect the tissues in different parts of the body, including the skin, muscle, joints and internal organs.

- ✓ Treatment of the underlying condition is recommended as well as treatment of PAH.

Pulmonary arterial hypertension associated with HIV infection

People with HIV may develop cardiovascular conditions, including PAH.

- ✔ People with PAH linked with HIV should receive antiretroviral treatment.
- 🔍 A single PAH drug should be considered for use first, before looking at combinations of medication. Healthcare professionals should carefully consider drug interactions and any other underlying conditions before deciding on a treatment plan.

Pulmonary arterial hypertension associated with portal hypertension

Portal hypertension is when there is an increase in pressure in the portal vein, which carries the blood from the bowel and spleen to the liver. A small number of people with portal hypertension (between 2 and 6 in every 100 people) will also develop PAH.

- ✔ Echocardiography is recommended for people with portal hypertension to look for signs or symptoms of PH. If people are found to have PAH linked with portal hypertension, they should be referred to centres that have expertise in both conditions.
- 🔍 A single PAH drug should be considered for use first, before looking at combinations of medication. Healthcare professionals should take into account underlying liver conditions and whether someone will need a liver transplant. Liver transplants should be considered on an individual basis depending on how stable PH symptoms are.

Pulmonary arterial hypertension associated with congenital heart disease

Congenital heart disease refers to a problem with the heart's structure that has been there since birth. For some people, surgery to repair the defect in the heart (known as shunt closure) is recommended.

- ✓ People with PAH that continues after the defect in the heart has been repaired should be assessed to look at what their risk is of developing a severe form of the condition.

Eisenmenger's syndrome refers to an advanced form of PAH linked with adult congenital heart disease.

- ✓ People with Eisenmenger's syndrome, or those with symptoms that persist after surgery to repair the heart, should be assessed to look at how severe their PAH is. The medication Bosentan is recommended for people with Eisenmenger's syndrome to improve their ability to exercise.
- 🔍 Oxygen therapy, iron tablets, endothelin receptor antagonists and prostacyclin receptor agonists, other PAH treatments and anticoagulant treatment may all be considered for people with Eisenmenger's syndrome depending on their specific symptoms.
- ✗ Pregnancy is not recommended for women with Eisenmenger's syndrome. Routine phlebotomy, where blood is regularly drawn out to lower levels of red blood cells, is also not recommended.



Pulmonary arterial hypertension associated with schistosomiasis

Schistosomiasis, also known as bilharzia, is an infection that affects around 200 million people worldwide, mostly in subtropical and tropical regions. Around 5 in 100 people with the “hepatosplenic” form of the condition develop PAH associated with schistosomiasis. There are no specific recommendations for this form of PAH. Data suggests the disease is not as severe as other forms of PAH and there are better survival rates.

Pulmonary arterial hypertension with signs of venous/capillaries involvement

The arteries carry blood pumped from the heart and the veins carry it back to the heart. The capillaries connect the two types of blood vessel. This subset of PAH refers to a form of the disease that also affects the small veins and the capillaries, in addition to the arteries.

- ✓ Diagnosis of PAH with signs of venous/capillaries involvement should include findings from a clinical examination, imaging results, lung function tests, gas exchange tests and genetic testing.
- ✓ Genetic tests that reveal a specific error in a person’s DNA (known as a genetic mutation) can confirm whether PAH with signs of venous/capillaries involvement is hereditary.
- ✓ Once a diagnosis is given, people who are eligible for a lung transplant should be referred to a transplant centre for evaluation.
- 🔍 Drugs that are approved for PAH may be considered along with monitoring of symptoms and gas exchange tests.
- ✗ Lung biopsy is not recommended to confirm a diagnosis.

Paediatric pulmonary hypertension

PH can affect people of all ages. Although there are some similarities with the adult disease, there are also important differences when both children and babies have the condition.

- ✓ Right heart catheterisation and vasodilator testing should be used to diagnose PH in children. Children should be treated at centres with specific experience of paediatric PH. The type of PH and how severe the condition is should also be confirmed. Once treatment has started, children should be monitored to see how they respond. The goal of a treatment plan should be to keep the risk of severe disease as low as possible.
- ✓ Babies should be checked for a condition known as bronchopulmonary dysplasia (BPD), which is often found as an underlying condition in babies with PH. If BPD is confirmed, treating this lung condition should be the first priority before starting treatment for PH.

Group 2: Pulmonary hypertension associated with left heart disease

People with PH associated with left heart disease have problems with the valves or muscle (myocardium) on the left side of the heart or issues with how the heart is pumping. Their arteries are not as thick as people in group 1 PAH, but there can be a build-up of blood as the left heart is unable to work quickly enough to pump the blood returning from the lungs.

- ✓ People with underlying heart conditions should receive treatment for this before being assessed for PH.
- ✓ Right heart catheterisation is recommended for people suspected of having PH associated with left heart disease to diagnose the condition before any surgery to repair the issues in the heart.
- ✓ If people are found to have a severe form of the disease, they should be treated in a specialist PH centre. Treatment plans should be tailored to each individual and close monitoring is recommended for people at risk of complications.
- ✗ Drugs approved for PAH are not recommended for people with PH associated with left heart disease.

Group 3: Pulmonary hypertension associated with lung diseases and/or hypoxia

This group includes people who experience PH because of a long-term lung condition or low oxygen levels. This includes conditions such as chronic obstructive pulmonary disease (COPD), where the airways are narrower, and pulmonary fibrosis where the lungs struggle to expand when a person breathes in. When these issues happen, the arteries in the lungs tighten causing high blood pressure in the pulmonary arteries.

- ✓ If PH is suspected in people with a lung condition, echocardiography is recommended and the results should be interpreted in conjunction with other pulmonary tests. Right heart catheterisation is recommended if the results can help with treatment decision making.
- ✓ Treatment plans should be tailored to each individual and should focus on the underlying lung disease and improving breathlessness and low oxygen levels. Referrals to specialist PH centres are recommended if there are uncertainties over treatments.
- ✓ Eligible people should be evaluated for possible lung transplants.
- ✗ PH medication is not recommended for people with lung conditions and mild or moderate PH.

Group 4: Chronic thrombo-embolic pulmonary hypertension (CTEPH)

This type of PH is caused by a chronic blood clot in the lungs. It occurs when your body cannot dissolve the blood clot and it leaves scar tissue in the blood vessels. This blocks the arteries making it harder for the heart to pump blood through them. This type of PH is unique as it can be treated by surgery to remove the blood clots. Other treatments could include a procedure to widen the pulmonary arteries with a balloon, known as balloon pulmonary angioplasty, or PH medication.

- ✓ Anticoagulation drugs are recommended for all people with CTEPH. Treatment plans should then be tailored to the individual and the type of disease they have. All people with CTEPH should also be referred to a specialist team for assessment.

Group 5: Pulmonary hypertension with unclear and/or multi-factorial mechanisms

This group refers to PH that happens alongside another condition or where it is unclear what is causing PH. It includes PH linked with sarcoidosis, sickle cell anaemia and certain metabolic disorders.

As there is a lack of research and evidence on how to treat this group, treatment is usually focused on the underlying condition linked with PH.

PH centres

While PH is not a rare condition, some forms of the condition require specialised care for the best outcomes. PH centres can provide this. The purpose of a PH centre is to look at what is causing PH, understand the type of PH a person has and look at the best way to manage it.

- ✓ PH centres should provide care by a team of experts from different areas of medicine – including heart and lung professionals along with nurses, radiologists and social workers.
- ✓ Centres should have plans in place to make quick referrals to other services, such as transplant units or genetic counselling services. They should also maintain a patient registry to help with research. It is also recommended that they work closely with patient organisations.

Patient associations and patient empowerment

Being diagnosed with, and living with, PH can be difficult. It is important that you are able to access any professional help you may need to manage any mental health issues you experience.

Patient associations can offer educational and emotional support to people diagnosed with PH. The guideline recommends that PH centres work with patient associations on initiatives to empower patients and improve the patient experience. They should work together on areas such as health literacy, digital skills, healthy lifestyles, mental health and self-management. By working together, healthcare can be delivered more effectively if people with PH are full partners in the process.

Further reading

This guideline was produced by the European Respiratory Society, the European Society of Cardiology and the European Lung Foundation. You can find out more about these organisations and access the full professional guideline using the links below:

Full clinical guideline

<https://doi.org/10.1183/13993003.00879-2022>

European Reference Networks (ERNs)

ERNs are networks of Centres of Expertise. They connect experts and researchers who share the same interests in specific rare diseases or highly specialised treatments. ERNs are patient-

centric and aim to improve cross border access to diagnosis, care and treatment. They do this by sharing their expertise, knowledge and resources to guide care and treatment. Within the ERN-LUNG is a PH Network that is working with 29 centres to offer guidance between countries and monitor standards at these centres. Find out more: <https://ern-lung.eu>.

Further resources for patients and carers:

European Lung Foundation factsheet on PAH: <https://europeanlung.org/en/information-hub/factsheets/pulmonary-arterial-hypertension/>

About ERS

The European Respiratory Society (ERS) is an international organisation that brings together physicians, healthcare professionals, scientists and other experts working in respiratory medicine. It is one of the leading medical organisations in the respiratory field, with a growing membership representing over 140 countries. The ERS mission is to promote lung health in order to alleviate suffering from disease and drive standards for respiratory medicine globally. Science, education and advocacy are at the core of everything it does. ERS is involved in promoting scientific research and providing access to high-quality educational resources. It also plays a key role in advocacy – raising awareness of lung disease amongst the public and politicians. www.ersnet.org

About ELF

The European Lung Foundation (ELF) was founded by ERS to bring together patients and the public with professionals. ELF produces public versions of ERS guidelines to summarise the recommendations made to healthcare professionals in Europe, in a simple format for all to understand. These documents do not contain detailed information on each condition and should be used in conjunction with other patient information and discussions with your doctor. More information on lung conditions can be found on the ELF website: www.europeanlung.org

About ESC

The ESC is a world leader in the discovery and dissemination of best practices in cardiovascular medicine. It is a volunteer-led, not-for-profit medical society; its members and decision-makers are scientists, clinicians, nurses and allied professionals working in all fields of cardiology. The ESC unites national cardiac societies from around the world; this unique network offers a unique understanding of the impact of cardiovascular disease and how we can better reduce its burden. For further information, please visit: www.escardio.org

