A Patient’s Guide to Understanding Pulmonary Arterial Hypertension in Systemic Sclerosis

Compared with the general population, patients with systemic sclerosis (also known as scleroderma) have a higher risk of developing a serious but rare condition called pulmonary arterial hypertension (PAH). This article explains key information about PAH, including the importance of being screened each year, what you can expect during an evaluation, and available treatment options.

What is PAH?
PAH is a disease of the blood vessels of the lungs, specifically the pulmonary arteries. PAH leads to a narrowing of the blood vessels as well as high blood pressure in the arteries that go from your heart to your lungs. This causes several symptoms such as shortness of breath, fatigue, and fainting.

PAH is a possible complication of systemic sclerosis, which is an inflammatory autoimmune disease (meaning that the body makes antibodies that attack its own tissues). People with systemic sclerosis can experience scarring in the skin and the body’s internal organs and tissues (for example, the muscles and nerves). Scarring can also affect the small blood vessels, causing poor circulation to the fingers and toes, and the large blood vessels of the lungs, resulting in PAH. About 8% to 12% of people with systemic sclerosis develop PAH.

Am I at Risk of Developing PAH?
If you have been diagnosed with systemic sclerosis, it is important to talk with your doctor about being screened for PAH every year as part of your treatment plan. PAH is a serious complication, but there are several effective treatment options once it is diagnosed, and earlier treatment may prevent the disease from getting worse. If left untreated, however, PAH with systemic sclerosis can eventually lead to right-sided heart failure and death.

Certain complications of systemic sclerosis can increase your risk of PAH, including:
- Having anticentromere antibodies (antibodies common in systemic sclerosis, found through blood testing)
- Multiple telangiectasias (small dilated blood vessels at the surface of the skin)
- Ulcers on fingers or toes
- Low diffusing capacity on a pulmonary function test (this measures how well your lungs move gas into the blood)

In addition, PAH is more common in older individuals.

You might find it helpful to make a list of questions you want to ask your doctor at your next appointment. The tear-out sheet provides some basic questions to help get you started, which you can take to your next visit.
What are the Symptoms of PAH?
In its early stages, PAH can be asymptomatic, meaning that you may not have any noticeable signs or symptoms. This is one reason it is important for people with systemic sclerosis to be screened for PAH each year—patients may not know that they have it. However, some early warning symptoms could suggest PAH, including:

- Shortness of breath, with or without exercise
- Fatigue
- Chest pain
- Swelling of the ankles, legs, arms, or belly
- Feeling weak
- Lightheadedness and/or fainting

If you have any of the above symptoms, be sure to mention them to your doctor. Shortness of breath should always be discussed with your doctor, even if it is mild. Fatigue or low energy levels should also be mentioned. It is important to note that fatigue can be an overall symptom of systemic sclerosis even without PAH, but feeling more tired than normal or having fatigue with shortness of breath could mean that your lungs are not working properly.

Importantly, PAH screening is recommended even if you have no obvious risk factors or symptoms because patients diagnosed through screening can be treated earlier, which may prevent the disease from getting worse.

What can I Expect from a PAH Screening?
There is no one way to screen for PAH, so your doctor will probably use a combination of tools. You can expect your doctor to sit down with you to obtain a detailed medical history and assess your health, including gathering information about your level of physical activity and any problems that may be limiting your activity. In addition, your doctor will most likely run these 3 tests:

1. A blood test for a biomarker called N-terminal pro B-type natriuretic peptide (NT-proBNP)—this evaluates the stress on your heart and looks for signs of heart failure
2. A pulmonary function test (pictured below)—this measures how well your lungs move oxygen in and out of your body as well as how well the oxygen moves through the blood vessels of your lungs
3. A noninvasive procedure called transthoracic echocardiography—this creates an image of the inner workings of your heart and helps your doctor see whether your heart is functioning properly

You may also be asked to complete a 6-minute walk test as part of your screening. During this exercise-based test, your doctor will monitor your pulse and oxygen saturation rates (this is expressed as a percentage: the amount of oxygen your blood is carrying divided by the total amount of oxygen your blood could carry) as you walk, usually up and down a hallway, for 6 minutes. Your doctor may have you repeat this test at later appointments to check for any changes in your exercise capacity (the maximum amount of physical effort you can withstand) and lung function.

Your doctor may also screen you for PAH using the DETECT model, which was developed from a worldwide study. It tests several variables (for example, forced vital capacity [FVC]/diffusing capacity for carbon monoxide [DL_{CO}] ratio, telangiectasias, anticentromere antibody, serum NT-proBNP, serum urate, and right axis deviation on electrocardiogram).
Depending on the results of these tests, your doctor may want to perform a more complex and precise test called right heart catheterization, which is needed to make a diagnosis of PAH. This is an outpatient procedure in which a catheter (a small, hollow tube) is inserted into the right side of your heart. The catheter measures the pressure in the chambers of the right side of your heart and the pulmonary arteries. It also measures how much oxygen is in your blood and the amount of blood that your heart pumps. This information creates a more accurate picture of how well your heart is functioning and whether there is increased pressure in the pulmonary arteries.

**What Treatments are Available?**
Although there is no cure for PAH, more treatments are available now than ever before. In addition, the earlier PAH is diagnosed, the better the chances for delaying the disease from getting worse.

Because every patient is unique, your doctor will tailor your treatment plan to your specific characteristics and the risks and benefits of available therapies. Your treatment plan will likely include both drug and non-drug therapies.

**Available Medicines for PAH**
Several drug classes are currently approved by the US Food and Drug Administration to treat PAH. When taken either alone or in combination, these drugs improve exercise capacity and blood flow in patients with PAH.

**Prostanoids (epoprostenol, iloprost, and treprostinil).** Epoprostenol and treprostinil both work by adding prostacyclin (a hormone) back in the blood vessels, which can help lower pulmonary blood pressure and improve blood flow to the lungs. Epoprostenol is given intravenously (into the veins) and continuously through a catheter and infusion pump. Iloprost is given by inhalation. Treprostinil can be given by continuous subcutaneous injection (under the skin), by inhalation, or by mouth.

**Endothelin receptor antagonists (ERAs) (ambrisentan, bosentan, and macitentan).** ERAs work by blocking the actions of endothelin (a peptide that narrows blood vessels) in the lungs, which can help lower pulmonary blood pressure and improve blood flow to the lungs. ERAs are all taken by mouth. One possible major side effect of bosentan (but not the other ERAs) is liver injury, so monthly blood tests are recommended for patients taking this medication. These drugs should not be part of your treatment plan if you are pregnant or planning to become pregnant because they may be dangerous to a developing fetus.

**Phosphodiesterase inhibitors (sildenafil and tadalafil).** These drugs work by enhancing the effects of nitric oxide, a substance in the body that helps lower pulmonary blood pressure and improve blood flow to the lungs. Both of these drugs are taken by mouth.

**Guanylate cyclase stimulators (riociguat).** Riociguat is the first drug in this new class approved to treat PAH. It works in a different way to enhance the effects of nitric oxide. Riociguat is taken by mouth. It should not be taken while pregnant or planning to become pregnant.

**Prostacyclin receptor agonists (selexipag).** Selexipag is a prostacyclin receptor agonist (activates the prostacyclin receptor) that lowers blood pressure in the lungs. It helps delay PAH from getting worse and lowers the risk of hospitalization due to PAH. Selexipag is taken by mouth.

**Combination therapy.** Combinations of the above drugs (taking more than one medication at a time) are often used. Together, you and your doctor can choose the best options for you.
# PAH - Pulmonary Arterial Hypertension

The following table provides key information about the medications described on the previous page.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>How It’s Taken</th>
<th>Benefits</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostanoids</td>
<td>Epoprostenol</td>
<td>Continuous injection into the veins (intravenous)</td>
<td>Improve exercise capacity and blood flow</td>
<td>Headache, diarrhea, jaw or bone pain, flushing (red face), infection at catheter site</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Inhalation several times a day</td>
<td></td>
<td>Headache, diarrhea, jaw or bone pain, flushing (red face), dizziness, nausea</td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>Continuous injection under the skin</td>
<td></td>
<td>Diarrhea, flushing (red face), headache, pain (jaw, hand, or foot), nausea</td>
</tr>
<tr>
<td></td>
<td>Ambrisentan</td>
<td>By mouth once a day</td>
<td>Improves exercise capacity; lowers blood pressure in the lungs</td>
<td>Swelling, flushing (red face), sinusitis, nasal congestion</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>By mouth twice a day</td>
<td>Improves exercise capacity, increases blood flow, and lowers blood pressure in the lungs</td>
<td>Liver injury, flushing (red face), headache, nose or throat irritation</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>By mouth once a day</td>
<td>Lowers blood pressure in the lungs</td>
<td>Headache, sore throat, congestion, swelling</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Sildenafil</td>
<td>By mouth three times a day</td>
<td>Improves exercise capacity and increases blood flow</td>
<td>Indigestion, flushing (red face), nose bleeds, vision changes</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>By mouth once a day</td>
<td>Improves exercise capacity and increases blood flow</td>
<td>Headache, upset stomach, back or muscle pain, congestion, flushing (red face), pain in limbs, vision changes</td>
</tr>
<tr>
<td></td>
<td>Riociguat</td>
<td>By mouth three times a day</td>
<td>Increases exercise capacity; widens blood vessels</td>
<td>Diarrhea, dizziness, indigestion, headache, nausea</td>
</tr>
<tr>
<td></td>
<td>Selexipag</td>
<td>By mouth twice a day</td>
<td>Delays PAH from getting worse and lowers the risk of hospitalization</td>
<td>Headache, diarrhea, jaw pain, flushing (red face), nausea, myalgia, vomiting, pain in extremities</td>
</tr>
</tbody>
</table>

## Non-Drug Treatments for PAH

Your doctor may also recommend some or all of the following non-drug treatments in addition to the medications described above:

- Supplemental oxygen can help keep the oxygen saturation rates in your blood above 90%
- Diuretics (also known as “water pills,” which help your body get rid of water) may be prescribed to reduce swelling of the ankles, legs, arms, or belly that can happen with PAH
- Anticoagulants (blood thinners) may be prescribed for those with more advanced PAH
- Supervised exercise training can increase your ability to exercise and improve mood and overall quality of life
A lung or heart/lung transplant may be an option for some patients who do not do well on medications. A number of factors determine who might need a transplant and who would be a good candidate. For example, certain systemic sclerosis symptoms like gastroesophageal reflux (when stomach contents return to the esophagus) or esophageal dysmotility (irregular contractions in the esophagus) might increase the risk of aspiration (substances from the stomach entering the lungs during surgical anesthesia), infection, transplant rejection, or other complications.

Whatever treatment plan you and your doctor choose, you should see your doctor frequently (every 3 months) and communicate any changes, positive or negative, that you notice in your overall health. If you are not noticing any improvements, your doctor may want to change your medications or your treatment approach.

How Will PAH Affect My Life?
Patients often find that coping with PAH and PAH medications affects their physical, social, and emotional life. Problems with moving your body and taking part in exercise can take its toll on both your body and your mood. You may notice an increase in feelings like anxiety, depression, or stress. These feelings are common. To help you through these challenges, it is important to try to create a physical and emotional support system of caregivers, friends, and family members. If you can, it might be helpful to surround yourself with people who you feel comfortable discussing not just the physical challenges but also the social, emotional, and financial challenges of coping with PAH. You may also want to find a patient-support group to build relationships with people who are dealing with similar issues.

Patient Resources and Support Groups

- Scleroderma Foundation: Offers tools and resources for patients with systemic sclerosis (also known as scleroderma) and their families (www.scleroderma.org)

- Pulmonary Hypertension Association: Offers resources and support for patients with pulmonary hypertension (https://phassociation.org)

- Some PAH drug manufacturers have patient-support resources—you can contact them directly (visit their Web sites for more information)
Be sure to talk openly with your doctor about your concerns, and do not be afraid to ask questions. He or she may be able to prescribe additional medication or suggest non-drug treatments to help with problems such as depression or poor sleep quality.

A successful PAH treatment plan will play a key role in improving your overall quality of life. The better you feel physically, the more positive you will feel emotionally as well.

What do I Need to Remember?
PAH is a serious condition that requires treatment. However, an early diagnosis can help you achieve the best possible outcomes. Here are some key things to remember:

1. Get screened by your doctor for PAH each year
2. If you are diagnosed with PAH, be in touch with your doctor and healthcare team regularly and work together to come up with a treatment plan
3. Take your medications as prescribed and follow your treatment plan
4. Assemble a network of friends, family, and caregivers who can provide physical and emotional support as you learn to manage your PAH
Do You Have Systemic Sclerosis?
Do You Know About Your Risk of Pulmonary Arterial Hypertension?

Compared with the general population, patients with systemic sclerosis have a higher risk of developing a serious but rare condition called pulmonary arterial hypertension (PAH). PAH may affect 1 in 10 patients with systemic sclerosis. Although PAH is a serious condition, several treatments are available to help manage it.

Do you have questions about PAH? If so, this resource can help you talk to your doctor. Tear it out and bring it with you to your next appointment. You can write down any additional questions you might have on the back of this sheet.

1. Have I been screened for PAH?

2. Why do I have a risk of developing PAH?

3. What symptoms should I tell you about right away?

4. If I have PAH, what are my treatment options?

5. Will I have to see another doctor if I have PAH?

6. Are there any clinical trials that I can join?

7. Can you tell me about patient-support groups in my area?

8. What online resources do you recommend?

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