

Chronic Rejection (Chronic Lung Allograft Dysfunction-CLAD) Following Lung Transplant

Chronic rejection is a major complication after lung transplant, affecting more than half of patients that survive beyond five years after transplant. Chronic lung allograft dysfunction (CLAD) is a term developed to encompass the different manifestations of chronic rejection that can occur in lung transplant recipients. Bronchiolitis obliterans syndrome (BOS) is the most common form of chronic lung transplant rejection.

What is BOS and what are the symptoms?

BOS typically occurs as a late complication of lung transplant, but in rare cases can occur as early as three months following transplant. BOS is a type of chronic rejection characterized by destruction of the (small) airways and narrowing and scarring of the airways within the donor lung(s). This scarring leads to progressive decline in the function of the transplanted lung(s). Initially a person may not experience any symptoms, but as time goes on common symptoms that may develop are:

- Shortness of breath (especially with activity)
- Fatigue
- Cough, sometimes with increased mucus production


These symptoms are also similar to those that develop during an infection. This is why it is important to report any new symptoms or problems to your lung transplant team so that a proper diagnosis can be made, as the treatment is quite different.

What are the risk factors for BOS?

It is not clear why some patients who receive a lung transplant develop BOS or develop BOS sooner than others. Some of the factors that are thought to play a role are things in the environment that irritate or damage the lungs, such as infection, air pollution or tobacco smoke, stresses related to the transplant operation itself, and the recipient's immune response to the transplanted lung(s). Some known risk factors for the development of BOS include:

- Primary graft dysfunction—This is when the transplanted lung is injured during the process of retrieval from the donor and/or implantation into the recipient and does not function properly early after surgery.



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- Acute cellular rejection or antibody-mediated rejection: Prior episodes of these forms of rejection can predispose an individual to develop BOS later.
- Gastroesophageal reflux disease (GERD)—This is when fluid from the stomach (either acidic or non-acidic) comes back to the throat and gets into the lung. This is a frequent problem in people who have lung transplants and needs to be treated to reduce lung injury.
- Certain infections increase the risk of BOS. These include:
 - Bacteria: *Pseudomonas aeruginosa*
 - Viruses: Cytomegalovirus (CMV) and common respiratory viruses
 - Fungus: *Aspergillus*

How is BOS diagnosed?

In the period right after transplant, recipients undergo regular checkups to make sure that lung function is stable and to monitor for complications. One of the common tests done at each of these appointments is lung function testing (spirometry). The value of the forced expiratory volume in one second (FEV1) in spirometry is most often used to help indicate how well the lungs are functioning and establish the best baseline values for the new lungs in the early months following the transplant operation. Knowing your baseline FEV1 after transplant is important, because if there is a decline or drop in your FEV1 or other spirometry numbers, it may indicate a problem, such as BOS, and your lung transplant team will perform a workup to determine the cause. Before BOS can be diagnosed, other causes for the decline in spirometry numbers or symptoms, such as infection and other forms of rejection, must be ruled out. When a drop in FEV1 persists, several other tests will be done before the transplant physician will formally diagnose BOS. The FEV1 is also used in the clinical staging system for BOS to define how it is progressing in a given person.

This workup may include:

- Lung Function Testing (spirometry)—Repeating the lung function test to examine the trend (for example, is the lung function improving, staying stable, or declining?).

- **Imaging**—A chest x-ray or chest CT (computed tomography) scan is performed to assess for evidence of occult infection. Occasionally, certain patterns of abnormalities on the CT scan may also raise the concern for rejection.
- **Bronchoscopy**—This procedure may be done to take samples from the lung to check for infection or other types of rejection.
- **Blood work**—Lab tests may be done to check for signs of infection or antibody-mediated rejection. A cell-free DNA (cfDNA) blood test may be used to see if the immune system is attacking the transplanted lung.

Your transplant team will work with you on what tests are needed. The final decision about a diagnosis of BOS is based on the transplant specialist's judgment and the results of testing to exclude other potential causes of the decline in FEV1. If there is no infection or other forms of rejection and the lung function tests do not recover or continue to decline, the diagnosis is likely BOS. The severity of BOS is determined by comparing the current FEV1 to the person's best FEV1.

What is the treatment for BOS?

The most important thing for preventing the development or progression of BOS is to try to reduce the risk factors as much as possible. It is also especially important to act quickly when lung function starts to drop. Important steps include:

- Promptly treating any bacterial, viral, or fungal infections that may arise.
- Promptly treating any acute rejection episode.
- Effectively treating GERD (acid reflux). If there is concern for GERD that does not respond to medications, your healthcare provider may order specific tests for GERD and/or recommend an anti-reflux surgery or procedure to help prevent any further lung injury.

Some people may be prescribed long-term azithromycin, an antibiotic that may reduce inflammation, which may help slow or reverse the decline in lung function. All transplant patients receive anti-rejection medications (immunosuppressants). If a patient develops BOS on one immunosuppression medicine, sometimes switching or adding other immunosuppressive therapy may help prevent further loss of lung function. Additionally, your transplant center team may try therapies such as extracorporeal photopheresis (ECP) or total lymphoid irradiation (TLI), or may discuss available clinical trial options. There are new treatments for BOS being developed and research continues into how to prevent and treat it.

Sometimes despite doing all the above, BOS continues to progress, and lung function continues to decline. If the BOS becomes severe enough and does not respond to any other therapies, the patient may have to be evaluated for a second lung transplant.

The clinical course after the diagnosis of BOS can vary a lot. Some people will have a progressive decline in lung function and develop respiratory failure, while others may remain stable for a long time. There is no straightforward way to predict the course of BOS over time for a given person, so close follow-up and excellent communication with your lung transplant team is important.

Other Forms of Chronic Lung Allograft Dysfunction (CLAD)

While BOS is the most common type of chronic rejection after lung transplantation, we have recently discovered other forms of chronic rejection. Emerging research suggests some patients may develop a form of chronic rejection termed restrictive allograft syndrome (RAS). While BOS is characterized by destruction and scarring of the (small) airways within the donor lung, RAS is characterized by predominant destruction and scarring of the air sacs (or alveoli) within the donor lung. This scarring is accompanied by a decline in lung function values, including not only the FEV1 (as in BOS) but also the forced vital capacity (FVC) or total lung capacity (TLC).

A CT scan of the chest with RAS may show new changes consistent with lung scarring. As with BOS, the diagnosis of RAS depends on the exclusion of other factors that could explain the decline in lung function, such as infection or other forms of rejection. While research is ongoing, the risk factors for developing RAS may be similar to those for BOS. Unfortunately, RAS is typically a more aggressive form of chronic rejection compared with BOS, and close follow-up is particularly important. Further research is needed to clarify the best treatment approaches to RAS, however in general, the management at this time is like that discussed for BOS. ●

Action Steps

- Monitor your lung function closely through home spirometry or in-office spirometry as recommended by your lung transplant team.
- Talk with your lung specialist and primary healthcare provider if you develop a decline in your lung function, shortness of breath, fatigue, or cough. Let your lung transplant team know right away.
- Discuss with your healthcare provider if you feel you have acid reflux symptoms that are not being controlled with medicines.
- Take your immunosuppression medicines regularly as prescribed by your lung transplant specialist and let the lung transplant team know if you have any side effects.
- Avoid air pollution, tobacco smoke exposure, and exposure to infection as much as possible.

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Additional Information

American Thoracic Society

- www.thoracic.org/patients

Flexible bronchoscopy

Lung function testing

Rejection after Lung Transplant

The Lung Transplant Foundation

- <https://lungtransplantfoundation.org/resources/chronic-rejection/>