

Bronchiolitis Obliterans Syndrome (BOS) Following Lung Transplant

Lung Transplantation Mini-Series #4

BOS is a lung problem that can occur after lung transplantation and is the most common form of chronic lung transplant rejection. Up to half of lung transplant recipients develop BOS within five years of transplantation. When BOS develops, a person will have a progressive loss of lung function when compared to the highest function after transplantation.



Although the initial symptoms may sometimes mimic those seen from a lung infection, BOS is not due to infection.

The main change seen with BOS is scarring of the small airways of transplanted lung(s). This scarring leads to narrowing of the airways, limiting airflow with loss of lung function. Early after the onset of BOS, a person may not have any symptoms, but will develop breathlessness and chronic cough as BOS gets worse. There are different stages of BOS based on lung function results. Some people develop an early stage of BOS and progress to more severe stages over a short time period, while others may remain stable in a stage for an extended periods of time. There is no clear way to predict the course of BOS over time for a given person.

What are the risk factors for BOS?

It is not clear why some transplant recipients (those who receive a lung transplant) develop BOS sooner than others. Some of the factors that are thought to play 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. The injured lungs right after transplant generally need more support for a longer period of time than usual.
- **Lung Rejection**—Rejection can be caused by the immune cells in the recipient's body or by antibodies that the body makes against the transplanted lung. Either form of rejection of the transplanted lung leads to a higher risk of BOS. (For more information on lung transplant rejection, see the ATS Patient Information Series "Rejection after lung transplantation".)

- 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 common problem in people who have lung transplant and needs to be treated to reduce lung injury.
- Certain infections increase the risk of BOS. These include:
 - Pseudomonas aeruginosa, a bacteria
 - Cytomegalovirus (CMV), a virus
 - Aspergillus, a fungus
 - A number of common respiratory viruses, including respiratory syncytial virus (RSV), parainfluenza, and influenza.

What are the symptoms of BOS?

Early after the onset of BOS, a person may have no symptoms as he or she still has very good lung function. This is why it is so important to keep close follow-up with the transplant team and get frequent lung function monitoring after the transplant. Transplant recipients become symptomatic from BOS because of decreased lung function. Common symptoms include:

- Shortness of breath
- Decreased exercise or activity tolerance and endurance
- Fatigue
- Cough, sometimes with increased mucus production

BOS is not an infection itself, but sometimes patients can have BOS and a respiratory infection at the same time. In that case, a person may also have fevers or chills. It is always important to look for other problems that can be treated.

How is BOS diagnosed?

In the period right after transplant, recipients undergo regular checkups to make sure that lung function is stable and there is no infection.

- **Lung Function**—one of the key lung function tests used in diagnosing BOS is the forced expiratory volume in 1 second (FEV₁), which measures the amount of air you can blow out in the first second of a forced exhalation.¹ The FEF_{25-75%} is another measure of lung function test (called “spirometry”). Over the first several months after transplant, spirometry is measured at regular intervals to establish the baseline value for the new lung(s). After this time (usually about three months), any sustained drops in FEV₁ raise the concern for BOS. When a drop in the FEV₁ persists, several other tests will be done before the transplant physician will formally diagnose BOS.
- **Imaging**—A chest x-ray or a CT is performed to rule out infection. Occasionally, certain patterns such as air-trapping or a new infiltrate (spot) may raise concern for rejection.
- **Bronchoscopy**—your transplant provider may decide to do this procedure to take samples from the lung. This procedure will include taking samples from the lung including fluid (bronchoalveolar lavage or BAL) and a tissue biopsy. The BAL involves squirting sterile fluid into the lung through the scope and suctioning it back out to send for tests. These tests mainly look for infection. The airway biopsies use a special forceps through the scope to get small pieces of airway tissue. These are looked at by a pathologist for any signs of rejection. It should be noted that biopsies obtained with bronchoscopy are not sensitive enough to always identify changes of BOS. The final decision about a diagnosis of BOS is based on the transplant physician’s judgment and the results of testing to exclude other potential causes of the decline in FEV₁.

If there is no infection or acute rejection, the diagnosis is likely BOS and the severity of BOS is determined by comparing the FEV₁ to the person’s usual (called baseline) FEV₁. The table below summarizes the different stages (Grade) of BOS.

BOS Grade	FEV ₁ % of predicted
0	>90*
0-p	81-90**
1	66-80
2	51-65
3	≤50

*Also must have another lung function measure, the forced expiratory flow (FEF_{25-75%}) greater than 75%
 **Also must have FEF_{25-75%} less than or equal to 75%

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 very important to act quickly when lung function starts to drop. Important steps include:

- Promptly treating any bacterial, viral or fungal infections that may arise, including those that stem from dental problems.

- Promptly treating any acute rejection episode with a short term treatment, usually high doses of corticosteroids and other medications, as decided by your transplant team.
- If there is concern for GERD that does not respond to medications, your health care provider may order specific tests for GERD and/or recommend an anti-reflux surgery 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 immunosuppression therapy (the medications that help keep the recipient’s immune system from attacking the transplanted lung). If a patient develops BOS on one immunosuppression medicine, sometimes switching or adding other immunosuppressive therapy may help prevent further loss of lung function. There are new treatments for BOS and research continues in how to prevent and treat it.

Sometimes, despite doing all of 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.

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Rx Action Plan

- ✓ Talk with your lung specialist and primary healthcare provider. If you develop shortness of breath, fatigue or cough, let your lung transplant team know right away.
 - ✓ Discuss with your health care provider if you feel you have GERD 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.
- Healthcare Provider’s Contact Number:**
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For Additional Information:

- American Thoracic Society**
www.thoracic.org/patients
- The Lung Transplant Foundation**
<http://lungtransplantfoundation.org/chronic-rejection/>
- Second Wind Lung Transplant Foundation of St Louis**
<https://secondwindstl.org/who-we-are/articles-by-dr-hacheem/>
- Duke Recent Lung Transplant Research**
<http://pulmonary.medicine.duke.edu/about-division/division-programs/lung-and-heart-lung-transplant-program/recent-lung-transplant-resea>

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¹ For more information on doing lung function testing, see the ATS patient information series “Lung Function Testing”



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