

Rejection after Lung Transplantation?

Lung Transplantation Mini-Series #3

The natural response of our body is to defend itself from harmful foreign substances like bacteria. However, in case of lung transplantation, the donor lung is recognized as the foreign substance. Rejection is a process by which your body's immune system attacks the transplanted lung, recognizing it to be different from your own tissues.



You must take medicines to reduce your natural immune response and 'trick' the body into accepting the new lung(s). Even with these medicines however, rejection can still happen.

How does the body recognize the donor lung as different?

Your body's natural immune cells are able to recognize small, unique proteins called "antigens" that are present on the surface of all cells or infectious particles. These immune cells, called the T cells and the B cells, can recognize the antigens as "self" if they belong to you or "non-self" if they do not belong to you (such as those in the donor lung). This recognition occurs mainly through complex proteins on the cell surface called "HLA antigens". The HLA system is made up of three classes with many subtypes. Each person has a combination of these HLA proteins that makes him or her unique—a signature. The differences in these signatures help our immune cells to separate "self" from "non-self". They then direct an attack on the foreign donor lung, resulting in "rejection".

Are there different types of rejection?

Rejection can be classified by how the immune system attacks the donor lung and the time after transplant when it occurs.

"Cellular rejection" occurs when your immune T cells directly attack the donor lung tissue. An "antibody mediated rejection" may occur where the recipient's B cells produce antibodies that attack the donor lung. These antibodies that develop in some patients can be detected by blood tests (called "donor-specific antibodies" or "DSA"). Cellular rejection is more common early on after transplant. Both of these types of rejection need to be diagnosed by a combination of testing, such as spirometry, x-ray imaging, and/or invasive testing like bronchoscopy (See "Flexible Bronchoscopy" and "Pulmonary Function Tests" at www.thoracic.org/patients).

Rejection can happen at any time after lung transplant. Just over a third of all lung transplant recipients will develop "acute rejection" within the first year after transplant. Acute rejection is the most common type of rejection. This is a change that develops over a short time and may resolve with prompt treatment. Over time, you may develop slowly worsening, chronic rejection called chronic lung allograft dysfunction (CLAD). A common form of CLAD is called bronchiolitis obliterans syndrome (BOS), which is the leading long-term cause of death one year after lung transplantation. (For more information see "Bronchiolitis Obliterans Syndrome Following Lung Transplant" at www.thoracic.org/patients).

Sadly, a majority of lung transplant recipients develop some form of chronic rejection over the years after transplant. This is a serious problem and may lead to progressive damage and loss of function in the transplanted lung.

What brings on rejection?

While rejection is a natural response of the body to anything foreign ("non-self"), there are some things that can make it more likely for rejection to occur.

The common factors include:

- infections that involve the lung e.g., cytomegalovirus (CMV) infection, fungal infection (like *Aspergillus*) and bacterial infections (like *Pseudomonas*).
- injury to the lungs that happens during and immediately after the transplant surgery (called 'primary graft dysfunction').
- not taking immunosuppressive medicines regularly and following your treatment plan after transplant.
- gastro-esophageal reflux disease (GERD).

You should report any new or increased symptoms promptly to your transplant provider. Watch for symptoms of acid reflux such as heartburn, acid taste in your mouth or

frequent stomach upset. Report any signs or symptoms of infection (like fever, fatigue, new or worsening cough or shortness of breath) promptly to your healthcare provider.

How do I know if I have rejection?

Unfortunately, rejection can develop silently without obvious symptoms. This means it can start and progress without warning. In some cases, you might notice symptoms like shortness of breath, cough or a low-grade fever. This is why you should report any new or worsening symptoms to your transplant team right away.

The best way to detect rejection is by monitoring of your lung function with regular breathing (lung function) tests and with bronchoscopy. You will be required to have periodic bronchoscopies with tissue biopsies after your transplant to look for early rejection even if you do not have a change in lung function or symptoms.

Antibody-mediated rejection (AMR) is diagnosed by a combination of symptoms, x-ray imaging, blood work for antibodies, and tissue biopsies. Your transplant team will have you get blood tests from time-to-time to check for specific antibodies against the donor lung made by immune cells, which helps assess the risk for antibody mediated rejection. Worsening of your lung function, along with development of new antibodies against the donor strongly increases the suspicion for AMR.

Chronic rejection is usually diagnosed by pulmonary function testing in combination with your symptoms. Usually there is a progressive worsening of your lung function. Your transplant team may decide to do other testing such as x-ray imaging and a bronchoscopy to rule out other causes of worsening in your lung function.

How is rejection treated?

Acute cellular rejection is treated in a number of ways depending on the severity and the number of episodes. Transplant centers also vary in their approach to treating acute rejection. Mild rejection is usually treated with high dose corticosteroids, which are initially given intravenously followed by a decreasing oral dose in pill form. More severe acute rejection can be treated with additional medicines that will strongly inhibit your immune cells. These may include rabbit antithymocyte globulin (RATG) or alemtuzumab (Campath®). You may be admitted to the hospital for a few days to treat rejection. You usually will have follow-up pulmonary function testing and a repeat bronchoscopy with biopsy a few weeks later to make sure the rejection is adequately treated.

If your transplant specialist suspects that you have antibody mediated rejection (AMR), he or she may elect to treat this by different methods, based on the severity and center preference. The various methods to treat AMR include removal or suppression of antibody production. Removing antibodies can be done by plasmapheresis, where a cannula (a large catheter) is inserted into a large vein and the plasma (along with the antibodies) is removed

and replaced by albumin. Treatments directed at reducing antibody production include giving a protein intravenously (IV) called immunoglobulin G (IVIG) and medications like rituximab and bortezomib (Velcade®), that reduce the number of B cells may be used. A repeat blood test, to check for antibodies is done a few weeks later to see how well these treatments worked.

A person can have multiple episodes of acute rejection over time. Repeated episodes of acute rejection increase the risk of developing chronic rejection. For more information on the management of chronic rejection, see “Bronchiolitis Obliterans Syndrome Following Lung Transplant” at www.thoracic.org/patients.

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Rx Action Plan

- ✓ Take all doses of your immunosuppression therapy as prescribed by your transplant specialist. Missing doses of these medicines put you at high risk of rejection.
- ✓ If you have concerns about any side-effects of the medicines, report them to your lung transplant team before stopping the medicine.
- ✓ Avoid contact with infectious material as much as possible by proper hand washing and avoiding sick contacts.
- ✓ If you develop shortness of breath, fatigue, cough or fever, let your transplant team know promptly.
- ✓ Report symptoms of gastroesophageal (acid) reflux to your lung transplant team.
- ✓ Ask your transplant specialist about different treatments for rejection, as there are choices and a unique treatment plan is chosen for each person.

Healthcare Provider's Contact Number:

For Additional Information:

The Lung Transplant Foundation

<http://lungtransplantfoundation.org/chronic-rejection/>

ATS Patient Information Series—Pulmonary Function Tests

<http://www.thoracic.org/patients/patient-resources/resources/pulmonary-function-tests.pdf>

ATS Patient Information Series—Fiberoptic Bronchoscopy

<http://www.thoracic.org/patients/patient-resources/resources/fiberoptic-bronchoscopy.pdf>

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