

## Rejection after Lung Transplantation

Lung transplant can give people with failing lungs another chance at life. The new lungs are at risk of damage from infections and/or rejection over time. This fact sheet describes types of acute rejection and the risk of chronic rejection after lung transplant. The immune system is a complex network of specialized cells that work together to defend the body against foreign elements (such as infections). It is a kind of 24/7 surveillance system that is always on the lookout for foreign elements to fight and destroy in an effort to keep the body safe. This works well when it comes to things we don't want in the body, like bacteria or viruses. However, it can be hard to manage when we need the immune system to accept a donor lung rather than reject it.



### How does the immune system recognize the donor lung as different?

Rejection is a process by which your body's immune system attacks the transplanted lung, recognizing it to be different from your own tissues. Every cell and tissue in the body contains small proteins on its surface. These proteins are called human leukocyte (or HLA) antigens. Each person has a unique combination of HLA antigens to themselves—like your signature or fingerprint. Specific cells of the immune system (T cells and B cells) recognize these antigens on the cell surface as either “self” if they belong to you or “non-self” if they don't belong to you (such as bacteria, viruses, or the donor lung). If the T cells and/or B cells recognize the donor lungs as “non-self” they can attack the lung; this is called rejection.

Luckily, there are medications which help “hide” the donor lung from the body's immune system. These are known as “anti-rejection” medications. These medications reduce your natural immune response and “trick” the body into accepting the new lung(s). Unfortunately, even with these medicines, rejection can sometimes still occur.

### Why does rejection occur?

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.

Common risk factors for rejection include:

- Infections that involve the lung from viruses like cytomegalovirus (CMV), SARS-Cov-2 (COVID-19), and influenza, bacteria like *Pseudomonas*, and/or fungi like *Aspergillus*. People with transplant continue to be at higher risk of severe infection and death from COVID-19 even as new variants emerge.
- Injury to the lungs that happens during and immediately after the transplant surgery (called ‘primary graft dysfunction’).
- Gastro-esophageal reflux disease (GERD).
- Not taking immunosuppressive medicines regularly or closely following your treatment plan after transplant.

You have to control your immune system, so it is very important to not stop or change any of your medications without first talking with your transplant team. Contact your transplant team right away if you have signs or symptoms of:

- infection such as fever, chills, fatigue, cough or shortness of breath.
- acid reflux such as heartburn, acid taste in your mouth, frequent stomach upset

- problems taking your medicines.

Prompt treatment can lessen the risk of developing rejection or detect rejection at its earlier stages.

### Can I have rejection starting without knowing it?

At times rejection can develop silently without obvious symptoms. This means it can start and progress without warning.

The best way to detect rejection and to catch it early is by monitoring your lung function with regular pulmonary function testing (spirometry) at home and in the clinic or lab. You also will need to have periodic bronchoscopies with biopsies of the donor lung tissue after your transplant. This will help detect rejection even if you do not have a change in lung function or symptoms.

### How is rejection diagnosed?

Your transplant team uses several tools to diagnose rejection. Your transplant specialist will ask you about your symptoms. You will have tests that may include spirometry, lung imaging (x-ray or CT scan), blood tests, and/or bronchoscopy. (See “Flexible Bronchoscopy” and “Pulmonary Function Tests” at [www.thoracic.org/patients](http://www.thoracic.org/patients)). Biopsies obtained during bronchoscopy are examined to see the type and severity of rejection.

### What are the different types of rejection?

#### How are they treated?

There are several different types of rejection and sometimes more than one type of rejection can occur at the same time. Rejection can occur at any time after transplant. The type is classified by how and when the immune system attacks the donor lung (Table 1).

#### Acute Cellular Rejection

Acute cellular rejection is the most common form of rejection. In the first year following lung transplant; about 30% of lung transplant patients will have at least one episode of acute cellular rejection. Acute cellular rejection can happen at anytime following lung transplant, but is much more common early on. This type of rejection occurs when the body's T cells directly attack the donor lung tissue.

Acute cellular rejection can be treated in a number of ways depending on the severity of the rejection, and how many episodes or occurrences a person has had. Mild rejection is usually either monitored closely without treatment or treated with high dose corticosteroids often at home (methylprednisolone or prednisone given IV or by mouth). More severe acute rejection can be treated with additional medicines that will more strongly

**Table 1: Overview of types of lung transplant rejection**

Type of Rejection	Immune System Response	Risk factors	Timing	Treatment
Acute Cellular Rejection	The body's T cells attack the donor lung directly	Infections, Acid Reflux, not taking medications as prescribed	Any time following transplant, but more common in the first post-transplant year	Monitoring only, steroids, rabbit antithymocyte globulin (RATG) or alemtuzumab (Campath®)
Antibody Mediated Rejection	The body's B cells produce antibodies which attack the donor lung	Prior pregnancies, prior transplants, and blood transfusions	Any time following transplant	Plasmapheresis, immunoglobulin G (IVIg), rituximab, and/or bortezomib (Velcade®)
Chronic Rejection (CLAD)	Persistent inflammation from the immune system over time causing scarring in the lung	Prior acute episodes of rejection, infections, acid reflux, not taking medications as prescribed	Any time following transplant, but more commonly after the first post-transplant year has passed	Preventing other types of rejection, azithromycin, montelukast, extracorporeal photopheresis (ECP) and/or clinical research trials

inhibit your immune system. These may include rabbit antithymocyte globulin (RATG) or alemtuzumab (Campath®). You may be admitted to the hospital for a few days for treatment. After treatment, you usually will have follow-up spirometry and a repeat bronchoscopy to make sure the rejection responded to treatment.

**Antibody Mediated Rejection**

Antibody mediated rejection is another type of rejection that can occur anytime following lung transplant. In this type of rejection, the body's B cells produce antibodies to the HLA antigens on the donor lung cells. These antibodies (called "donor-specific anti-HLA antibodies" or "DSAs") attack the donor lung tissue and damage it. DSAs can be detected by blood tests.

Antibody mediated rejection can be treated in several different ways. The treatment depends on various factors including the severity of the rejection being caused by the antibodies. Treatment may involve the removal of harmful antibodies from the circulation or suppression of harmful antibody production by eliminating the immune cells that produce them (B cells and plasma cells). Removal of antibodies can be done through a procedure called plasmapheresis, where a large catheter or IV is inserted into a vein (typically in the neck or groin region) and the antibodies are "cleaned" or removed from the blood. Suppression of antibody production can be accomplished by using certain medications such as immunoglobulin G (IVIg), rituximab, bortezomib (Velcade®), or similar medications that reduce the number of antibody producing B cells or plasma cells in the body. Following treatment, a repeat blood test to check for remaining antibodies may be done and your spirometry will be monitored closely.

**Rejection: The Big Picture and Chronic Rejection**

Rejection can happen at any time after lung transplant. Either type of rejection is a change that develops over a short time and may resolve with prompt treatment. Unfortunately, in some people rejection can be difficult to treat or may not respond well to treatment(s).

Over time, you may develop persistent worsening of your lung function. This may represent chronic rejection, also known as chronic

lung allograft dysfunction (CLAD). This is a serious problem and may lead to progressive damage and loss of function in the transplanted lung. Sadly, a majority of people who have had lung transplant do develop chronic rejection over the years after transplant. For more information on chronic rejection and its management, see "Chronic Rejection (Chronic Lung Allograft Dysfunction—CLAD) Following Lung Transplant" at [www.thoracic.org/patients](http://www.thoracic.org/patients).

Working together and talking about any new symptoms or concerns with your lung transplant team is the best way to keep your new lungs healthy!

**Action Steps:**

- ✓ Take all doses of your immunosuppression therapy as prescribed by your transplant specialist. Missing doses of these medicines puts 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.
- ✓ Monitor your lung function regularly through home spirometry or as advised by your lung transplant team.
- ✓ Avoid contact with infectious agents as much as possible by proper hand washing and avoiding sick contacts. Talk to your transplant specialist about vaccines you can take to help fight infections like COVID-19 and influenza.
- ✓ If you develop shortness of breath, fatigue, cough, fever, or a decline in your home spirometry numbers 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 often a unique treatment plan is chosen for each person.

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**Resources:**

**American Thoracic Society**

- <https://www.thoracic.org/patients>
  - Flexible bronchoscopy
  - Lung function testing
  - Chronic rejection- CLAD

**The Lung Transplant Foundation**

- <http://lungtransplantfoundation.org>

**National Health Service- UK**

- <https://www.nhs.uk/conditions/lung-transplant/risks/>

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