

The Immune System

Infection and rejection after a lung transplant

This handout explains how the immune system works, and why it must be suppressed after lung transplant surgery.

What is the immune system?

The *immune system* is a complex network of special cells and organs. When it is working well, it protects the body against “invaders” such as viruses, bacteria, fungi, and other infections.

To do this, the immune system must tell the difference between a person’s own cells and any invading “non-self” cells. If the immune system finds “non-self” cells, it will attack them. This is a type of *immune response*.

An immune response can be triggered when the immune system finds *antigens* in the body. Antigens are often “non-self” cells. They might be cells from bacteria, viruses, or other types of infection.

Antigens can also be cells from another person, such as blood used in a transfusion or an organ used for a transplant. The immune system sees these substances as “foreign” and tries to remove them. When this happens after an organ transplant, it is called *rejection*.

How does the immune system work?

When the immune system senses antigens, it activates *white blood cells* to fight the invader. The 2 main types of white blood cells are *lymphocytes* called *T cells* and *B cells*:

- **T cells** attack the foreign cells directly.
- **B cells** produce *antibodies* that attach to the foreign cells. These antibodies signal other immune cells to attack the foreign cell.



As a transplant recipient, you will take medicines to suppress your immune system, to keep it from rejecting your new lung(s).

What stops the immune system from rejecting a transplanted organ?

Transplant recipients are given medicines to suppress their immune system and keep it from rejecting the transplanted organ. These are called *immunosuppressants* or *immunosuppressive medicines*.

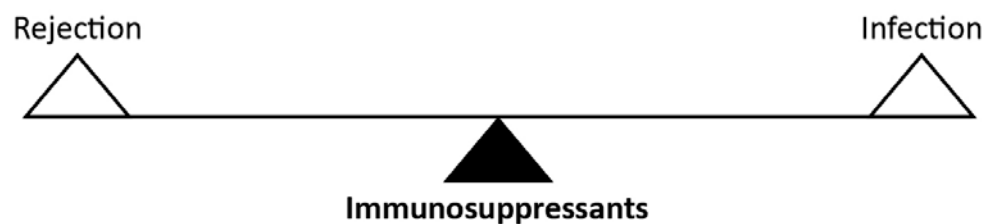
Lung transplant recipients start to receive these medicines when they go to the operating room for the transplant surgery, even before the donor lung(s) are placed in their body. After the transplant surgery, recipients must take immunosuppressants for the rest of their lives.

Challenges in Suppressing the Immune System

Your immune system must be suppressed to prevent rejection of the transplanted lung(s). But if your immune system is suppressed too much, it will not be able to fight infections. Both rejection and infections threaten your overall well-being and the health of your transplanted organ.

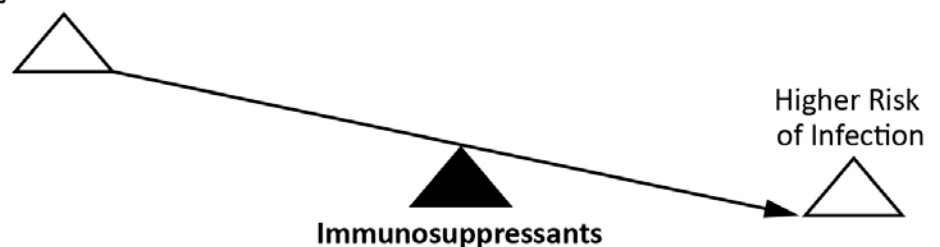
Once you have your new lung(s), we want to both keep your body from rejecting the new lung(s) and limit your risk of infection. We will do our best to adjust your immunosuppressant doses to find the right balance. This process takes time.

These drawings show the relationship between immunosuppressants, rejection, and infection:

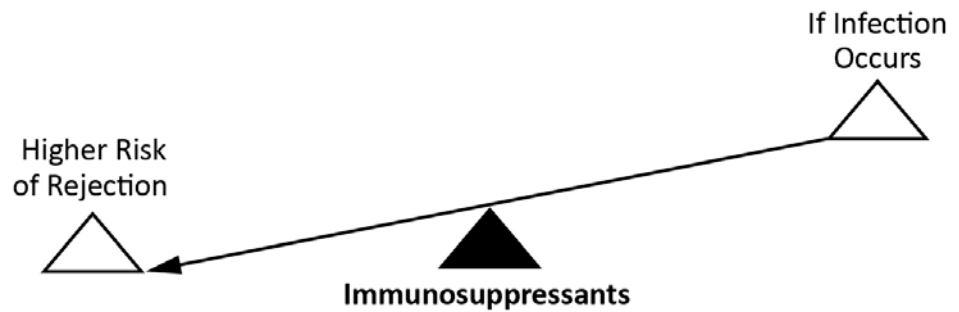


When well balanced, immunosuppressant medicines prevent rejection and infections are minimized.

If Rejection Occurs



If rejection occurs, we will increase the level of immunosuppression. This increases the risk of infection.



If an infection occurs, we may decrease the level of immunosuppression. This increases the risk of rejection.

We will closely monitor your lungs and overall health after surgery. If needed, we may adjust your doses of immunosuppressants at your follow-up visits. This is one reason you must have follow-up visits very often in the first few months after transplant surgery.

How long will I need to take immunosuppressants?

Every lung transplant recipient must take immunosuppressive medicines every day for the rest of their life. This is because the recipient's body will never accept the transplanted organ as its own. As long as the recipient is alive, there is always a risk of rejection. The amount of immunosuppressive medicines varies, depending on each lung transplant recipient's unique situation after the lung transplant surgery.

Does the risk of rejection change over time?

Most times, rejection occurs during the first 12 months after a lung transplant. But it can occur at any time, even many years after the transplant surgery.

Right after a lung transplant, the recipient receives high doses of immunosuppressants. This high dose is needed right away to keep the immune system from rejecting or damaging the new lung(s). As time passes, the immune system may become less aggressive in its attempt to reject the new lung(s). If this happens, we may be able to reduce the level of immunosuppressive medicines over time.

If rejection occurs at any time after a lung transplant, your level of immunosuppression will need to be increased. After we treat you for rejection, we may need to find a new balance of immunosuppressive medicines to keep you from having another rejection episode.

What are the symptoms of rejection?

It is not always easy to diagnose rejection after a lung transplant. Symptoms of rejection might include:

- Decrease in *spirometry* (breathing tests), particularly FEV1
- Shortness of breath
- Fever
- Changes in chest X-ray or *computed tomography* (CT) images
- Change in oxygen saturation
- New fatigue

These symptoms can also occur if you have an infection or other problems after a lung transplant. If you have any of these symptoms, we may ask you to have a test called a *bronchoscopy* to help us find the cause.

During a bronchoscopy, a scope is inserted into your lung(s) through your nose or mouth. This allows us to look at the new lung(s) and take samples to test for rejection, infection, or other problems.

What happens if rejection occurs?

Treatment of rejection depends on whether it is *acute* rejection or *chronic* rejection, also called *chronic lung allograft dysfunction* (CLAD).

Acute Rejection

There are 2 main types of acute rejection:

- *Acute cellular rejection*, usually triggered by T-cells
- *Antibody-mediated rejection*, usually triggered by B-cells

If we find rejection or we feel strongly that your symptoms are being caused by rejection, your level of immunosuppression will be increased until the rejection subsides. Treatment depends on the type of immune cell most likely causing the rejection.

After acute rejection is treated, the patient's lung function often returns to their former baseline. But sometimes the transplanted lung(s) are damaged by the rejection episode. This can mean that the lungs will never work as well as they did before the rejection. The patient's symptoms after treatment of the rejection will depend on how severe the lung damage is.

Acute Cellular Rejection

Acute cellular rejection occurs when T-cells attack the new lung(s) directly. Most times, the first treatment given for acute cellular rejection is a “pulse” (short-term treatment) with high-dose steroid medicines (*methylprednisolone*, then *prednisone*).

If the rejection does not respond to this first treatment, we will try other ways to get rid of the T-cells that are causing the rejection. These other treatments can include medicines like *anti-thymocyte globulin* (ATG) and *alemtuzumab*, both of which kill T-cells. These drugs strongly suppress the immune system for a while. Sometimes, they can cause severe, permanent suppression of the immune system.

Antibody-mediated Rejection

Antibody-mediated rejection requires treatments directed at B-cells and the antibodies that are triggering an attack on the new lung(s). These treatments can involve some combination of:

- *Plasmapheresis*, a process that removes antibodies from the blood, much like dialysis removes toxins for patients with kidney failure
- *Rituximab*, a medicine that kills immature B-cells
- *Bortezomib*, a medicine that kills the mature B-cells that produce antibodies
- *Intravenous immunoglobulin* (IVIG), a medicine that inactivates circulating antibodies and decreases the production of new antibodies

Chronic Lung Allograft Dysfunction

Chronic lung allograft dysfunction (CLAD) is also called *bronchiolitis obliterans syndrome* (BOS) or *chronic rejection*. CLAD is defined as a *sustained* decline in spirometry (FEV1 and/or FEF 25% to 75%), without another cause.

CLAD occurs in most lung transplant recipients over time. We do not know why it occurs. There may be many factors that play a role, including:

- Episodes of acute rejection
- Episodes of infections, including respiratory viruses (colds and flu)
- Gastroesophageal reflux (GERD)

Sometimes, there does not seem to be a specific event that has caused CLAD to occur. And even when we manage and treat issues that could cause CLAD, we might not be able to keep it from occurring in lung transplant recipients.

It is very hard to diagnose CLAD. We do not have a test that clearly points to CLAD as the cause of a patient's symptoms or permanent decline in spirometry.

Studies show the most likely end-result of CLAD is damage to the *bronchioles* (very tiny airways in the lungs) and scarring of the lung tissue. The bronchioles become inflamed, causing them to be distorted, narrowed, and plugged with scar tissue. After the bronchioles are destroyed, the patient can develop severe *obstructive airway disease* (cannot get air out). When a lot of scar tissue forms, the patient can develop severe *restrictive lung disease* (cannot get air in).

We do not have medicines that can restore lung function after the bronchioles are destroyed. The best we can do is to try to keep more damage from occurring. We do this by treating any known underlying problems such as acute rejection, infection, or gastroesophageal reflux.

For lung transplant recipients, the best way to try to prevent CLAD is to:

- Take your medicines **exactly** as prescribed.
- Closely monitor your breathing with your home spirometry machine. Call the Lung Transplant office **right away** if you have a decline in FEV1 of more than 10% from your baseline.
- Keep in close contact with the UW Lung Transplant Team. Call the Lung Transplant office **right away** if you have any new symptoms.

Infections

After a transplant, the recipient takes immunosuppressants to prevent rejection. But suppressing the immune system lowers the body's ability to fight off infections. This means bacteria, viruses, or fungi can cause infections that don't often affect people with a normal immune system.

The air we take into our lungs may contain *infectious pathogens* (organisms that cause infection). This can be dangerous for someone whose immune system is suppressed.

Viruses

Viruses cause about 40% of infections (40 out of 100 infections) that occur in transplant recipients. Some infections are more common early after the transplant surgery, but others can occur at any time after a transplant.

Herpes Viruses

The *herpes virus* family is one of the most common causes of viral infections in transplant patients. By age 25, more than 80% of people (80 out of 100 people) have been infected by a herpes virus (cold sores, chicken pox, etc.).

When someone gets a herpes virus, the virus lives in their body for the rest of their life. These “latent” infections usually do not cause problems. But, when the immune system is suppressed, the herpes virus can reactivate or “wake up” and cause problems.

There are 4 types of herpes virus:

Herpes Simplex Virus (HSV)

HSV Type I (HSV-1) outbreaks often cause cold sores. Type II (HSV-2) outbreaks often cause genital herpes.

HSV outbreaks most often occur in the first 6 months after a transplant or up to 3 weeks after treatment for rejection. At these times, the patient is on higher doses of immunosuppressants. As the level of immunosuppression decreases over time, the number of HSV outbreaks also goes down.

Other factors which may reactivate HSV are stress, anxiety, other illness, friction, or chafing. Rarely, HSV infections can involve internal organs such as the lungs, liver, and brain. For patients who keep having HSV outbreaks, we may prescribe a daily anti-viral medicine.

Varicella Zoster Virus (VZV)

VZV causes both chicken pox and shingles. The first time you are exposed to VZV, you develop chicken pox (the *primary illness*). The reactivation of VZV is called shingles (the *secondary infection*).

Rarely, VZV infections can affect other organs such as the lungs, eyes, or brain. For patients who keep getting shingles, we may prescribe a daily anti-viral medicine.

Cytomegalovirus (CMV)

CMV is a common herpes virus that occurs in immunosuppressed patients. The risk of CMV infection after a lung transplant depends on the status of the donor (D) and recipient (R).

- A lung transplant recipient who has been infected with CMV (R+) can receive an organ from a donor who had also been infected with CMV (D+), or from a donor who had NOT been infected (D-).
- Likewise, a lung transplant recipient who has NOT been infected with CMV (R-) can receive an organ from a donor who had been infected with CMV (D+), or from a donor who had also not been infected (D-).

CMV infection can occur in any transplant patient. But, lung transplant recipients who have not had CMV infection (R-) who receive an organ from a donor who has been infected with CMV (D+) are at the highest risk of reactivation. This is because their bodies have not developed immunity to CMV, and the immunosuppressants often keep these patients from developing immunity to CMV. This makes it harder for their immune system to keep the CMV under control.

If either the lung transplant recipient or their donor has a history of CMV infection (R+ or D+), the recipient will receive a *prophylaxis* (preventive) dose of an anti-viral medicine such as *valganciclovir*. How long they receive this prophylactic medicine depends on the CMV status of the donor and recipient and whether a CMV infection occurs after transplant.

A blood test to check for CMV is done often during the first year after a lung transplant. Many times, we find CMV in the blood before the patient has any symptoms. CMV can also cause symptoms such as fever, severe fatigue, shortness of breath, abdominal pain, nausea or vomiting, or diarrhea.

If CMV is found, we will start treatment right away. If you have symptoms from CMV, we might do tests to see if the CMV is causing problems in your lung(s) or stomach and *gastrointestinal*

(digestive) tract. Treatment will continue until the CMV is gone. This can take 3 weeks to several months.

Epstein-Barr Virus (EBV)

EBV causes *mononucleosis*. It is also involved in *post-transplant lymphoproliferative disorder* (PTLD). This is a type of *lymphoma* (cancer of the lymph nodes) found in people who are taking immunosuppressants. PTLD is rare but most times can be treated.

Respiratory Viruses

Respiratory infections (colds) can occur after a lung transplant. Colds can be the same as they are for people who are not taking immunosuppressive medicines. But, lung transplant recipients might notice their symptoms are a little worse and last a little longer than in other people.

Sometimes respiratory viruses can cause major damage to the transplanted lung(s). They can even trigger acute rejection. If you get cold or flu-like symptoms after transplant surgery:

- Call the UW Lung Transplant Team **right away**.
- Watch your symptoms closely and use your home spirometry to monitor your lung function.

We do not have treatments for most respiratory viruses, but it is still important to tell us about any symptoms as soon as you can.

Bacterial Infections

About 40% of infections (40 out of 100 infections) that occur after a transplant are caused by bacteria. These infections can occur at any time after a lung transplant and may affect any part of the body. Watch yourself closely for any signs of infection.

If you notice any signs, call the UW Lung Transplant Team **right away**. We might do tests to help tell us what bacteria may be causing the infection. Once we know if bacteria are involved, we can decide the best treatment.

Fungal Infections

Fungi cause about 10% to 20% of the infections (10 to 20 out of 100 infections) that occur after an organ transplant. *Fungal spores* (pieces of the fungus) are normally found in the air. There are

usually more spores in areas where the soil has been disturbed, such as building sites, farming areas, and compost piles. If a transplant recipient is exposed to these areas often, and does not wear a mask or other protection, it can increase their risk of getting a fungal infection.

It is always a good idea to wear a mask and other gear to protect yourself when you are around areas where soil has been disturbed. This includes wearing long sleeves and long pants if your arms or legs might come in contact with the soil.

Aspergillus

The most common fungal infection after a lung transplant is *Aspergillus*. *Aspergillus* is a mold that is all around us. We all breathe in a few *Aspergillus* spores all the time. When there is a lot of dirt in the air, we may breathe in a large amount of *Aspergillus* spores at one time. This raises the risk of getting an *Aspergillus* infection.

Symptoms of *Aspergillus* infection can include fever, shortness of breath, or cough. We can also sometimes find it on a chest X-ray or *computed tomography* (CT) scan before symptoms appear.

Treatment for an *Aspergillus* infection can involve taking an anti-fungal medicine for at least 3 to 6 months.

Preventing Infections

Preventing infections is a good way to protect your health. Most of the things that help prevent infections make good sense.

Washing Your Hands

Simply washing your hands might be the very best way to prevent the spread of infection! Most people pick up respiratory viruses by touching things such as door handles, sink faucet handles, and grocery store carts and then touching their *mucus membranes* (eyes, nose, and mouth). It's easy to carry hand sanitizer and clean your hands when you are out in public and around objects that other people have touched.

Wearing a Mask

We advise transplant patients to wear masks at certain times to lower the risk of getting some types of infections. Remember to wear a mask:

- Whenever you return to the hospital or clinic. There are many sick people in the hospital who may cough or sneeze, so wear a mask!
- Anytime you are around building sites or any place where you can see dust or debris in the air.
- When you are digging soil in the garden or doing other yard work.

There may be other times we advise wearing a mask, such as during the outbreak of a disease such as COVID-19. Please talk with your transplant team to find out what to do during these times.

Tips to Prevent Infection

- Avoid being around anyone who is sick.
- Wash your hands often, especially when you are in public places.
- Use common sense if you do not feel well. Give yourself time to rest, eat healthy foods, and drink plenty of fluids. Call the UW Lung Transplant Team and tell them your symptoms. They could have other ideas of ways you can take care of yourself.

Vaccines

Before you receive a lung transplant, we will make sure you are up to-date on your vaccines.

Vaccines may include shots to prevent:

- Hepatitis
- Pneumonia
- Flu
- Tetanus and whooping cough (Tdap)
- Measles, mumps, and rubella (MMR)
- Shingles

After your lung transplant, we advise you to get a flu shot every year. It is also important to update your pneumonia vaccine. Ask the UW Lung Transplant Team how often you need to do this.

Warning About Live Virus Vaccines

Some vaccines contain live viruses. **After transplant, you must NEVER receive an immunization that contains a live virus.**

With your suppressed immune system, you may get the infection instead of being protected against it.

The most common live vaccines are for:

- Shingles
- MMR (measles, mumps, and rubella)

Other live vaccines include:

- *Intranasal* (nasal spray) flu vaccine
- Smallpox vaccine
- Oral polio vaccine
- Yellow fever vaccine

Questions?

Your questions are important. Call the UW Medicine Lung Transplant Team if you have questions or concerns:

Weekdays from 8 am. to 4 p.m.: Call 206.598.5668.

After hours and on weekends and holidays: Call 206.598.6190 and ask to page the Pulmonary Transplant fellow on call.