Rejection (the basics)- Consult your transplant team for more information

Rejection is a major problem after organ transplant. It occurs as a normal immune response to a foreign (non-self) tissue. Transplant teams minimize the possibility of rejection by checking blood type, crossmatching antibodies, and HLA antigen matching between donor and recipient at the time of the transplant. Since many HLAs exist, a perfect match is nearly impossible. Immunosuppressant medications play a major role in preventing organ rejection. Experts report that 90% of all transplant recipients experience some degree of acute rejection in the first few months after transplant but only 50% of recipients experience chronic rejection in the first 5 years after transplantation and 76% in the first 10 years (Bos et al., 2020; Hachem & Corris, 2018).

There are three types of rejection: hyperacute, acute, and chronic. Hyperacute rejection occurs within 24 hours of the transplant and is rare. It occurs because the recipient had pre-existing antibodies against the transplanted organ. Acute rejection is seen in the first six month after transplantation. This is usually a cell-mediated event but it could be humoral rejection. (If these are strange terms, go read the "Basics of Immunity" document on this web page.) It is common to have at least one episode of acute rejection. The treatment is to administer high dose steroids and increase the dose and types of immunosuppressants and it is usually reversible.

Chronic rejection, one of the major complications following lung transplantation, can occur any time after transplantation, The cause is often unknown but risk factors include repeated episodes of acute rejection, viral illnesses, CMV disease, frequent episodes of pneumonia. Sacreas, et al. (2018) suggested that it is a chronic humoral and cell-medicated response of the recipient's immune system towards the transplanted donor organ (the non-self cells). If this is unchecked, it can lead to scarring and fibrosis of the lung tissues and failure of the organ. At the cell level there are a large number of B and T lymphocytes. Chronic rejection post lung transplant is also called chronic lung allograft dysfunction (CLAD). CLAD can be one of two types: bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome (RAS) which the pathologist can differentiate as specific changes noted at biopsy. BOS is characterized persistent obstructive pulmonary function and air trapping. RAS is characterized by restrictive pulmonary function decline (Verleden et al., 2018).

For more information about the basics, check these sites:
https://www.youtube.com/watch?v=rznRZgsD3yk

https://www.youtube.com/watch?v=jToFFEXPw7k

Symptoms of lung rejection

These can be a vague feeling of fatigue or some symptom related to a decreasing lung function. Some signs include shortness of breath, persistent cough, fever, or an unexplained decline in the baseline pulmonary function studies. Chronic rejection is a process that can occur over months to years and cannot be reversed. In chronic rejection with transplanted lungs, the small airways thicken (Workman, 2017). There are 3 different patters noted with lung transplant recipients: 1) a

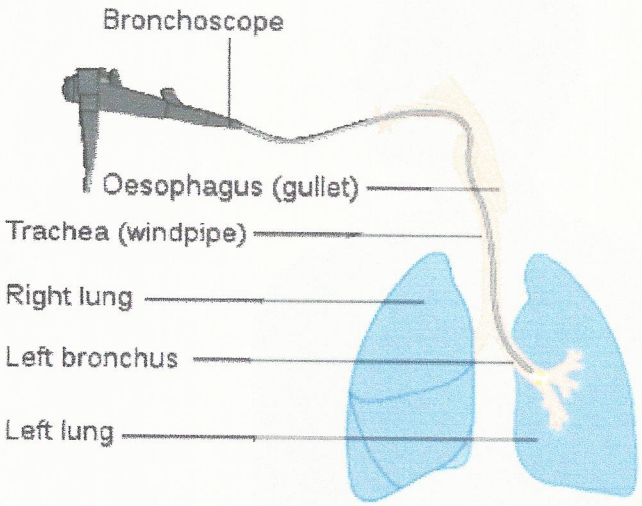
rapid onset with progressive decline, 2) rapid onset with initial decline, followed by stabilization and 3) rapid onset and decline (Coutre, 2001).

Diagnosing Rejection

A bronchoscopy to collect samples of lung tissues for biopsy is the outpatient procedure used to check for rejection and infection. The physician will pass a flexible tube through the nose or mouth into the trachea and down the two small air pages of the lungs. Sputum and tissue samples are collected to check for infection (bacteria, fungi, or viruses) and lung cells. The pathologist will grade lung specimens after examining them under a microscope. The stages are: none, minimal, mild, moderate, and severe.

Bronchoscopy Procedure

(clip art from Cancer Research UK / Wikimedia)



Typically, this procedure is pre-planned, but it can be done as an emergency procedure in the hospital. In preparation for this procedure, the patient must have nothing to eat or drink for 6 to 8 hours prior to bronchoscopy. Instructions will include information about continuing to take any blood thinners (anticoagulants), aspirin, and ibuprophen. Good mouth care should be completed (teeth brushing, mouthwash rinse, etc.) and any dentures removed. Alert your physician if there are any loose teeth. One should practice breathing through the nose with the mouth open so this strategy can be used during the procedure. Bronchoscopies can be done as an outpatient procedure, in a surgical suite, or at the bedside in the intensive care unit or hospital room. Shortly before the procedure the patient is usually given sedation to reduce any anxiety. The patient's

oropharynx or nasopharynx are anesthetized with a local spray and the lighted bronchoscope is lubricated with a water-soluble gel. The physician inserts the flexible tube (with a small camera at the end) through the nose or mouth into the small airways. A small amount (1 ounce or 30 cc) of sterile saline is injected into small airways of one lung lobe and then suctioned to collect a sample for testing. Mucous plugs can also be removed if they are present. After the procedure, the patient should sit in a semi-reclining position with the head elevated. After a few hours, the gag reflex will return and then the patient can drink fluids. Pink tinged sputum or a small amount of blood in the sputum is not a cause for concern. To reduce any discomfort after the gag reflex returns, the patient can gargle with warm salt water, drink warm fluids, and use throat lozenges. Many who have a sore throat find a soft diet helpful.

Treatment of rejection

The International Society for Heart and Lung Transplantation with other professional task forces provided practice guideline recommendations for the treatment of rejection but these are still under investigation (Meyer, 2018). Health care teams at each transplant center develop their own protocol based on the best available evidence. Initially, the dose and/or types of immunosuppressants are increased. There could be a trial of azithromycin. If gastric reflux is a problem, surgical interventions are considered to prevent further reflux. Another approach to reduce the antibody levels has been the intravenous administration of immunoglobins and rituximab, a drug that targets B-lymphocytes and destroys them. Plasmapheresis, where the plasma containing the antibodies and antigen-antibody complexes is removed, have helped slow the rejection process. Extracorporeal photopheresis has been shown to reduce pulmonary decline and also to stabilize lung function (Isenriing, 2018). As a final option, re-transplantation can be explored.

Immunosuppressants (oral medications)

Drug Class	Examples	Actions related to transplantation
Corticosteroids	Prednisone (Deltasone)	Inhibits cytokine production in leukocytes, reduces inflammation.
Calcineurin inhibitors	Cyclosporine (Sandimmune, Neoral, Gengraft) Tacrolimus (Prograf)	Prevents activation of lymphocytes
Antiproliferatives or Cytotoxic drugs	Azathioprine (Imuran) Mycophenolate (CellCept, Myfortic) Sirolimus (Rapamune) Everolimus (Afinitor, Zortress)	Inhibit DNA synthesis which prevents cell division in activated B or T lymphocytes

Extracorporeal Photopheresis (ECP)

ECP had been used successfully for more than 35 years with cancer patients but it has also been used with solid organ transplant patients in rejection in the last few decades (Cho et al, 2018). It is approved by the FDA. ECP is used after other interventions have been used but were as effective as desired. The purpose of this procedure is to inactivate the white blood cells (T-cells) that are causing the rejection. Initially, a quantity of blood is taken from the patient. The parts are separated by centrifuge by the photopheresis machine and then the red blood cells and plasma (liquid part) are returned to the patient. The white blood cells are treated in the lab with ultraviolet light and a medication, methoxsalen. Then, the treated white blood cells are returned to the patient. After reinfusion, the inflammatory process is reduced. Each transplant center determines the best schedule for their patients, but the typical treatment course is 1 cycle every 2 weeks for 2 months and then a monthly cycle (Hachem & Corris, 2018).

The procedure is completed on an outpatient basis. The transplant nurse coordinator will provide preparation instructions prior to the scheduled appointment. On the day of the procedure the nurse will insert the needle and tubing to collect the blood from either a peripheral vein (e.g., arm) or a central vascular catheter (e.g., PICC line). The tubing is connected to the photopheresis machine. The procedure takes about 3 hours to complete and nurses will monitor closely the patient's blood pressure and heart rate for any changes. After the procedure, the patient has a bandage at the needle site and can return home. Side effects include slight bruising at the needle site, low-grade fever that disappears in 24 hours, and sensitivity to sunlight (use sunglasses).

References

Bos, S., Vos, R, Van Raemdonck, D., & Verleden, G. (2020). Survival in adult lung transplantation: where are we in 2020?, *Current Opinion in Organ Transplantation*: 25 (3), 268-273. doi: 10.1097/MOT.0000000000000753.

Cho, A., Jantschitsch, C., & Knobler, R. (2018). Extracorporal Photopheresis-An overview. *Frontiers In Medicine*, 5. 236. doi:10.3389/fmed.2018.00236.

Hachem, R., Corris, P, (2018). Extracorporeal Photopheresis for Bronchiolitis Obliterans Syndrome after lung transplantation, *Transplantation,* 102 (7), 1059-1065. doi: 10.1097/TP.0000000000002168

Isenring, B., Robinson, C., Buergi, U., Schuurmans, M. M., Kohler, M., Huber, L. C., & Benden, C. (2017). Lung transplant recipients on long-term extracorporeal photopheresis. *Clinical Transplantation, 31*(10), e13041-n/a. doi:10.1111/ctr.13041

Ius, F., Verboom, M., Sommer, W., Poyanmehr, R., Knoefel, A., Salman, J., Kuehn, C., Avsar, M. Siemeni, T., Erdfelder, C., Hallensleben, M., Boethig, D., Schwerk, N., Mueller, C., Weite, T., Falk, C., Haverish, A., Tudarache, I., Warnecke, G. (2018). Preemptive treatment of early donor-specific antibodies with IgA- and IgM-enriched intravenous human immunoglobulins in lung transplantation. *American Journal of Transplantation, 18*(9), 2295-2304. doi:10.1111/ajt.14912

Meyer, K. C. (2018). Recent advances in lung transplantation. *F1000 Research, 7*, 1684. doi:10.12688/f1000research.15393.1

Verleden, S. E., Vos, R., Vanaudenaerde, B. M., & Verleden, G. M. (2017). Chronic lung allograft dysfunction phenotypes and treatment. *Journal of Thoracic Disease, 9*(8), 2650-2659. doi:10.21037/jtd.2017.07.81

Workman, M. (2016). Inflammation and Immunity. In D. Ignatavicius & M. Workman, *Medical-Surgical Nursing: Patient-centered collaborative care*, (8th ed. pp. 277-289) Elsevier.