



TRANSPLANT IMMUNOLOGY- AN OVERVIEW

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ABSTRACT

The process of replacing a cell, organ, or tissue with a healthy counterpart is known as transplantation. Every year, hundreds of organs, tissues, and cells are transplanted throughout the world. Human immunological reactions to the graft are the main obstacle to the transplantation of organs, tissues, and cells. The transplant will be rejected if the recipient's immune system rejects it because it is foreign. Recipients of immunosuppressive medications have an increased risk of infection and cancer because the drugs non-specific immune system inhibition. Longer transplant longevity is promised by new techniques being developed to induce particular tolerance to the graft without dampening other host immune responses. More transplant recipients are put on a lifelong combination immunological medication or steroid therapy to prevent graft rejection. Despite its toxicity and side effects, this medication does not work to stop chronic graft rejection. Additionally, immune suppressive drugs non-specifically weaken the immune system, increasing the risk of infections and cancer in their users. Longer transplant longevity is promised by new techniques being developed to induce particular tolerance to the graft without dampening other host immune responses. To keep improving transplant immunology, immunosuppression will require ongoing critical approaches, review, and customization. Additionally, longer-term immunosuppression-related comorbidities, primarily chronic kidney disease (CKD) and cancer, have increased as a result of improved survival after lung transplantation, necessitating more sophisticated management strategies.

KEYWORDS: Graft, Transplant, Donor, Recipient, Immune system, Hemopoietic system.

INTRODUCTION

Transplantation is the process of moving cells, tissues, or organs, from one site to another, either within the same person or between a donor and a recipient. If an organ system fails, or becomes damaged as a consequence of disease or injury, it can be replaced with a healthy organ or tissue from a donor. Organ transplantation is a major operation and is only offered when all other treatment options have failed. Consequently, it is often a life-saving intervention. In 2015/16, 4,601 patient lives were saved or improved in the UK by an organ transplant. Kidney transplants are the most common organ transplanted on the NHS in the UK (3,265 in 2015/16), followed by the liver (925), and pancreas (230). In addition, a total of 383 combined heart and lung transplants were performed, while in 2015/16.

However, whole organs are not the only type of transplant. The cornea, for example, is the most transplanted single tissue, with 5,734 procedures carried out in 2015/16. Hematopoietic stem cell transplantation (HSCT), often called blood and marrow transplantation (BMT), is another common tissue transplantation procedure. Used to treat a broad spectrum of diseases,

though most commonly for blood or bone marrow cancers such as leukemia and lymphoma, around 3,600 HSCT transplants were undertaken in 2012. The immune system plays a critical role in transplantation.

To reduce the possibility of rejection, the donor and recipient are carefully matched for immune compatibility prior to transplantation. However, the small pool of eligible donors can make it difficult to find a donor-recipient match and there will always be a degree of rejection against the graft.

There are various methods for tissue and organ transplantation:

Autograft

The transfer of cells, tissues, or organs from one part of the same person to another. Like a skin transplant.

Allograft

An allograft is when organs or tissues from a donor are transplanted into a non-genetically similar member of the same species. The most typical type of transplant is an allograft.

Xenograft

A xenograft is when an organ or piece of tissue is transplanted between two distinct species. For instance, human heart valves with defects are frequently repaired or replaced using "pig valves." The NHS performed 6,069 replacements of xenograft valves in England in 2015–16.

ABO incompatibility

Blood groups, or ABO, can differ from person to person. Matching blood groups between donors and recipients is crucial for the majority of transplant types.

Transplanting stem cells

In the body, stem cells have the potential to differentiate into a variety of distinct cell types. In order to replenish blood cells that have been damaged or lost, blood stem cells, also known as hematopoietic stem cells, are donated. Leukemia and other blood disorders where the bone marrow has been damaged and is no longer able to produce healthy blood cells are treated with hematopoietic stem cell transplantation.

TYPE OF TRANSPLANTATIONS**1. Organ transplantation**

Different organs can be transplanted:

- Pancreas
- Kidney
- Liver
- Lung
- Heart

2. HSC transplantation

Stages of HSC transplant:

- Decision to treat
- Donor search - Histocompatibility
- Conditioning
- Transplantation
- Reconstitution of hematopoiesis

3. Blood transfusion

Different blood components are transfused like Blood platelets etc.

IMMUNOLOGY OF PANCREAS TRANSPLANT

Diabetes, a condition marked by an imbalance in the homeostasis of glucose metabolism, is extremely common throughout the world and is associated with considerable morbidity and mobility issues because of vascular and neurological consequences. In incident patients receiving hemodialysis, it is the one factor that causes end-stage renal disease the most frequently. Depending on an etiology, diabetes has different clinical manifestations and epidemiology. The greatest therapy option for certain people to achieve glycemic control is pancreatic transplantation.^[1]

Single pancreas transplant

The ideal transplant would be an isolated pancreas transplant in diabetics without renal disease who also

have few or no secondary complications. By being able to stop the development of secondary problems, they would stand to gain the most from the good consequences of this transplant.

Acute rejection and technical problems (mostly graft thrombosis) are more common with organ transplants than with other types of surgery. Patients who require repeated hospital hospitalizations due to metabolic complications and have brittle diabetes with normal renal function receive it.

Severe hypoglycemia unawareness or decompensation.

Indications

Ignoring severe hypoglycemia (life-threatening)

Continual hospitalization for metabolic complications

Failure to regulate blood sugar levels while being admitted to the hospital using other methods, such as an insulin pump and/or continuous glycemic control monitors

Absolute prohibitions

- Severe coronary artery disease that is incurable.
- Prolonged hepatic or lung illness; severe left ventricular dysfunction.
- A current infection
- Active or former cancer without a sufficient duration of remission (excluded in situ and skin epitheliums).
- Serious physical or mental illness.

Contraindications relative

Age range: 18 to 55 years old, (BMI 30 kg/m²) Obesity

- Current acute coronary syndrome
- A recent bleeding in the retina
- Cerebrovascular or peripheral vascular conditions that are symptomatic
- Severe autonomic neuropathy or gastropathy caused by diabetes
- Current smoking

Pancreas After of Kidney transplantation (PAK)

The main advantage of PAK is that it shortens or eliminates the need for dialysis while waiting for a pancreas transplant in patients who are eligible for both a kidney and pancreas transplant and who have a living kidney donor available. Renal function recovery may lessen uremia-induced anticoagulation and perhaps lessen bleeding after surgical complications.^[2]

Long-term effects and difficulties

In recent years, pancreas transplant outcomes have improved, with a median graft survival of up to 15 years when utilizing current methods. Close ambulatory controls must be carried out during the first year in order to obtain these results, with the duration between outpatient visits being increased if follow-up is uneventful. It is typical to undertake a weekly control during the first three months following Tx, a weekly control till six months, and a monthly control between six and twelve months.

They concentrate mostly on immunosuppressive, functional graft monitoring, and problems related to diabetes. Each outpatient follow-up includes a determination of baseline glycemia, glycosylated hemoglobin (HbA1c), serum amylases, and serum lipases to evaluate pancreatic graft functionalism. It is easy to perform an oral glucose tolerance test (OGTT) in the post-transplant period, following hospital release, and once again one year after transplant. As a result, it is advised to conduct an annual ophthalmological examination.

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Treatment for maintenance

Three medications are most frequently combined as an adjuvant therapy to induction therapy and as long-term maintenance immunosuppression.

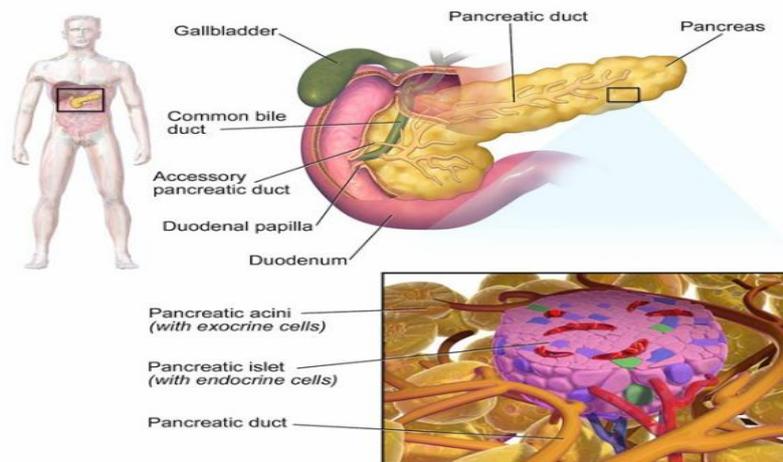


Fig. 1: Immunology of Pancreas Transplant.

An anti-perioperative medication, steroids, and a calcineurin inhibitor (CNI). When cyclosporine was discovered 35 years ago, a new era in solid organ transplantation began. Although there was an increased risk for renal calcineurin toxicity and consequent renal failure, the rate of acute rejection was significantly decreased, and patient and graft survivals showed a remarkable improvement.

Tacrolimus (or FK-506), a CNI as well, has an improved and more effective immunosuppressive profile, making it the preferred medication for pancreatic transplantation at the moment.

The first drug used, **azathioprine**, stops the cell cycle in the G2 phase, preventing it from continuing into the M phase and preventing clonal growth that follows.

Excellent outcomes have been seen with triple therapy, which uses one medication from each category. The most used combination is tacrolimus, mycophenolate, and

steroids. Mycophenolate may be substituted with a mTOR-inhibitor, although side effects must be carefully managed.^[4]

IMMUNOLOGY OF THE KIDNEY TRANSPLANT

The best form of renal replacement therapy for the majority of individuals with end-stage kidney disease continues to be a kidney transplant. Due to the global organ shortage, patients may be on the transplant waiting list for a period of years. Modern crossmatch methods and human leukocyte antigen (HLA) typing are essential for ensuring better organ allocation and a better match for the recipient. Due to the existence of all antigens and allorecognition by the recipient, organ transplantation into a person with a different genetic make-up would invariably result in an immunological reaction.

Crossmatch is still a crucial tool for identifying preformed monospecific antibodies in recipients who have already been sensitized to foreign antigens, despite the development of new and more potent

immunosuppressive regimens in the modern era of transplantation. The seminal article by Patel and Teriyaki first established the necessity of a crossmatch before kidney transplantation (1969). Since then, a positive CDC-XM has generally been regarded as a contraindication to transplantation due to the increased risk of hyperacute rejection that is linked with it. Tissue crossmatch serves as a valuable risk assessment tool for antibody-mediated rejection, which is a major impediment to enhancing long-term transplant outcomes.^[5]

CROSSMATCH TECHNIQUE

In the 1980s, flow cytometry crossmatch was created. It functioned as a more sensitive method to identify donor-specific antibodies that the CDC-XM was missing. The procedure involves incubating fluorescently conjugated anti-human globulin with recipient serum after adding recipient serum to donor cells. Later, additional antibodies with various fluorochromes tailored to the surface proteins of T-cells and B-cells, respectively, are added to distinguish both cell types. One benefit over the CDC-XM is that it provides a semi-quantitative result, which is less arbitrary. The flow cytometer is calibrated using a pool of sera from highly sensitized individuals as a positive control and serum from blood group AB unsensitized male donors as a negative control.^[6]

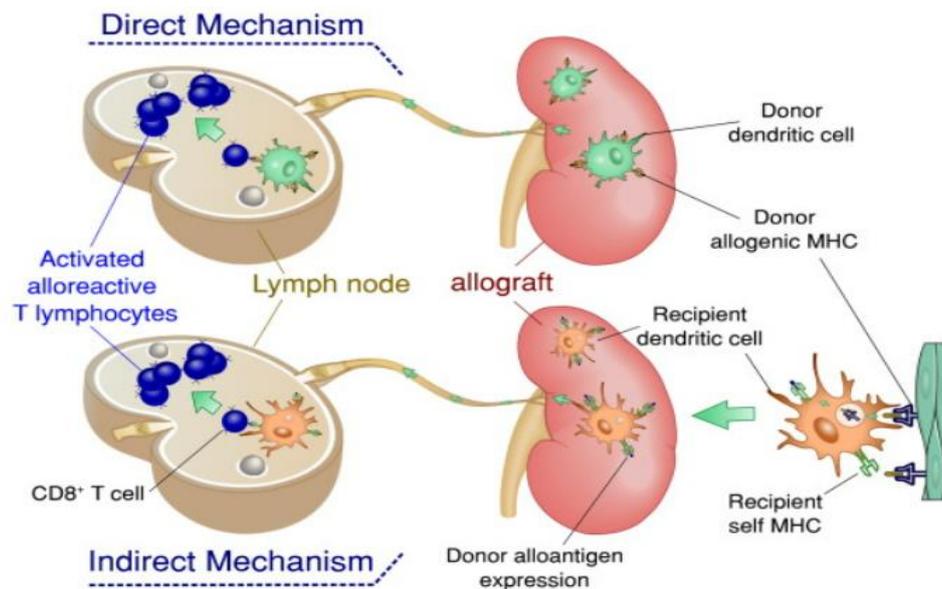


Fig. 2: Immunology of Kidney transplant.

IMMUNOLOGY OF LIVER TRANSPLANT

As an Immune Organ, the Liver

The liver is constantly exposed to a variety of significant antigenic loads because of its location and function, including infections, poisons, tumor cells, as well as dietary and commensal proteins. To be able to selectively develop immunity or tolerance to antigens, the liver must be actively immunocompetent and manage inappropriate inflammatory responses to dietary and other innocuous antigens encountered in the portal circulation. As early as 19678, hepatic inhibition of sensitization to antigen absorbed by the portal route was established.^[7]

The immunological phenotype of liver sinusoidal endothelial cells (LSECs), which display markers indicative of myeloid lineage cells, is distinct (CD1, CD4, CD11c). Antigen-presenting LSECs do not induce effector Th1 cell differentiation in CD4 T cells.^[8]

IMMUNOLOGICAL FACTORS IN CLINICAL LIVER TRANSPLANTATION

Most episodes of acute cellular rejection happen within 90 days of transplant surgery and affect 50% to 75% of

liver allograft recipients. The targets of activated lymphocytes are vascular endothelium and bile duct epithelial cells from donors; hepatocytes are rarely directly involved. The prevalence of chronic rejection has reduced over the past ten years, and it now affects less than 5% of patients.^[9]

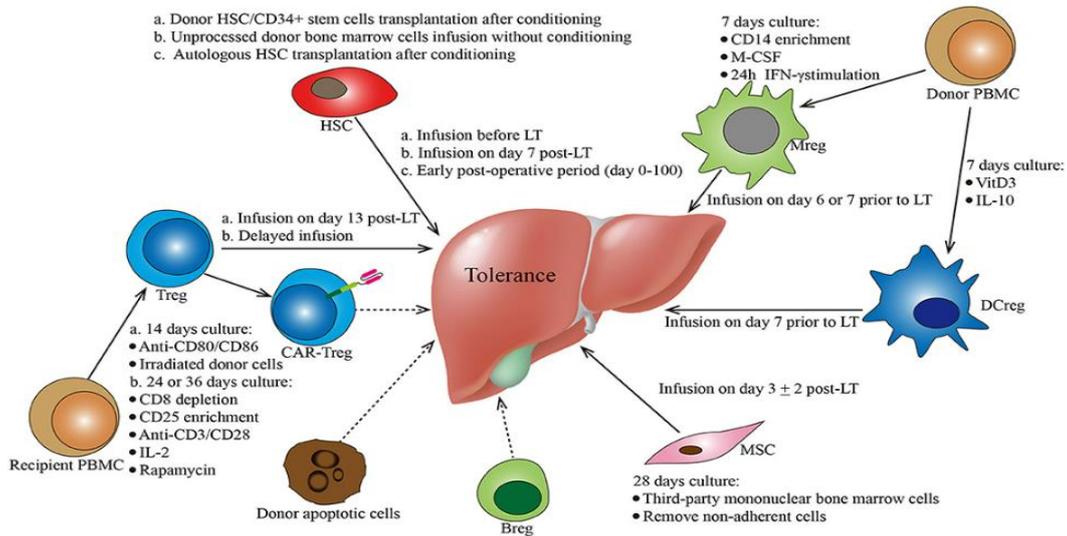


Fig. 3: Immunology of Liver transplant.

Chronic rejection, also known as "ductopenic rejection," is characterized by ischemia injury to and scarcity of bile ducts.

Theoretically, any transplanted organ is equally susceptible to the autoimmune process as the organ being replaced, since many disorders treated by liver transplantation are thought to be autoimmune in origin.^[10]

IMMUNOLOGY OF THE LUNG TRANSPLANT

Although lung transplantation (LTx) begins with intensive surgery in a patient with end-stage lung illness,

the long-term success of this therapy will likely eventually depend on the balance of intrinsic host immunity and extrinsic additional immunosuppressive techniques.

The following concerns are specific to the lung allograft

All immune-compromised patients have difficulties from exposure to the outside environment, the absence of lymphatic, bronchial arterial reconnection, or ciliary innervation, which serve as the primary sites of many infections.

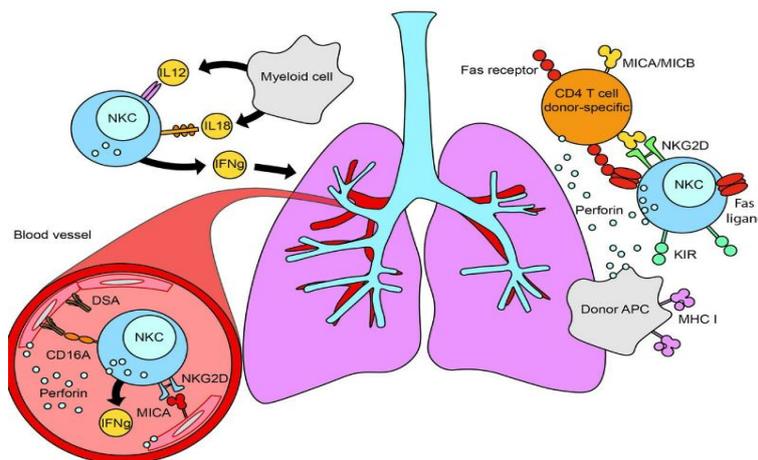


Fig. 4: Immunology of Lung Transplant.

Rejection following lung transplant

Extreme rejection

A summary of the many types of lung rejection is provided here. Within minutes or hours following the allograft's reperfusion, a fulminant form of lung rejection known as hyperacute rejection takes place.^[11] Hyperacute rejection is brought on by pre-formed donor-specific antibodies (DSA). Although non-HLA antibodies may potentially result in hyperacute rejection,

DSA are mostly directed against mismatched human leukocyte antigens (HLA). Hyperacute rejection is still rather uncommon, though.

It proves that antibodies can lead to fulminant allografts in which the capillary endothelium is specifically injured.

Rapid cell rejection

ACR, on the other hand, is a frequent side effect following lung transplantation. In the first year following transplantation, over 30% of adult lung transplant recipients in the ISHLT Registry experience at least 1 episode of ACR.^[12]

The degree of infiltration and extension into the nearby interstitial determines how severe ACR is.

Immune system-mediated rejection

AMR is a kind of lung allograft rejection that is becoming more well-recognized. Numerous case reports and case studies from various centers outlining the presentation and clinical characteristics of AMR have been published recently.^[13] A consensus definition for pulmonary AMR was created by the ISHLT based on these discoveries and expertise in kidney transplantation.^[14] This definition states that definite AMR is diagnosed when all of the following conditions are satisfied:

- Allograft clinical dysfunction
- Pathology of lung damage
- Capillary C4d synthesis
- Distributing DS
- Clinically ruling out any additional potential reasons of allograft malfunction.

The clinical presentation, DSA features, histologic findings, and outcomes of C4d-positive cases of AMR¹⁵ were compared to C4d-negative cases in a recent very sizable single center study. With the exception of the fact that C4d-negative instances were more likely to be caused by non-complement binding DSA, there were no significant differences between the two groups. The

authors suggested that instances of AMR that test negative for C4d be regarded as definite cases of AMR if all other criteria are satisfied.^[15]

IMMUNOLOGY FOR HEART TRANSPLANTS

One of the major illnesses that jeopardize human health and life is cardiovascular disease. The final step of many cardiovascular disorders, including hypertension, coronary heart disease, and valve heart disease, is heart failure. Around 37.7 million people suffered from heart failure globally in 2010. According to a different study, there are between 100 and 900 new cases of heart failure for every 100,000 persons annually.^[16]

Tolerance and heart transplantation for ABO-incompatible patients

Heart transplant recipients have already benefited from tolerance. The most important development in pediatric heart transplantation in the last 50 years has been the use of tolerance to increase the number of pediatric cardiac donors available through ABO-incompatible heart transplantation.^[16] Immune assays performed thereafter have consistently revealed low antibody generation against all of the donor blood type antigens.

Obstructed transplantation

- Transgenic complement control proteins - xenotransplantation - missing self (NK cells, complement).
- Organ transplantation - recognition of non-Self (natural antibodies) - ABO-matching
- Modified self (unknown MHC-peptide complexes), organ and HSCT, leading to HLA-matching.^[17]

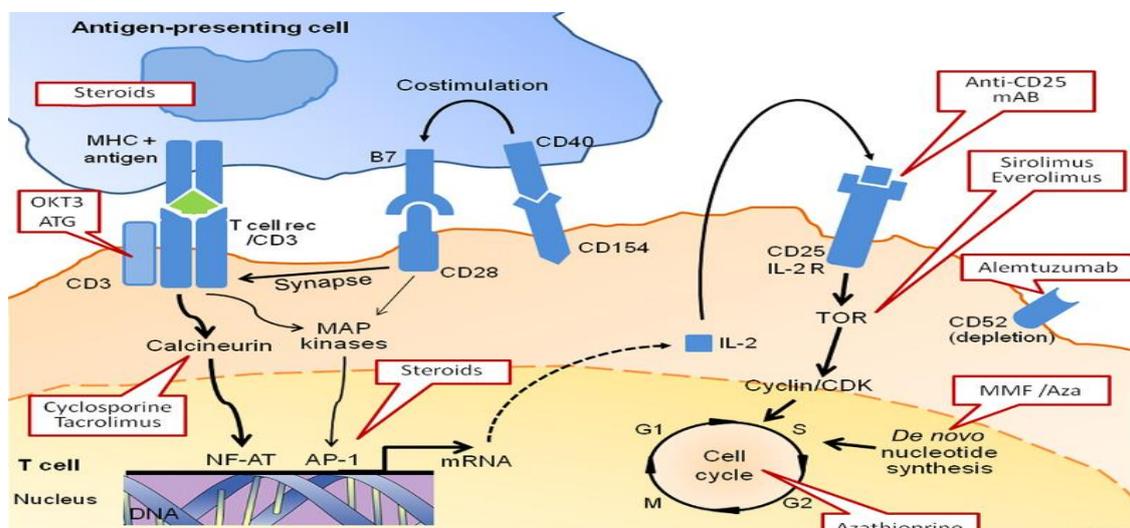


Fig. 5: Immunology of Heart Transplant.

CONCLUSION

Immunosuppression regimens have changed from a standard recipe to fit all types into a nuanced and tailored individualized approach to balance the risk of immunosuppression against the competing risk of

rejection as increasingly complex transplanted candidates have been successfully transplanted and improved survival in these patients. This calls for careful consideration of the numerous inherent host factors that are specific to a single recipient, as well as of their

perioperative course and immunosuppressant side effects. Comorbidities and CLAD should also be minimized, as well as overall excellent long-term transplantation outcomes. Immunosuppression strategies will need to continue to evolve and be tailored as our knowledge of the numerous complicated aspects involved in allograft failure grows, along with novel developing molecular and biomarker assessments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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