In The Name of God
Introduction

- Solid organ transplantation is a well accepted therapeutic option for patients with end-stage kidney, liver, heart, & lung disease. For many of these patients, it is the only option.

- Although transplantation has had a significant positive impact on the quality of life in most patients with end-stage disease, issues such as retransplantation because of graft failure or recurrence of disease, donation source (living-related & unrelated-neonatal organs, animal organs), & costs to individuals, insurers, & society continue to be discussed vigorously.
Milestones In Organ Transplantation
1954  Surgeons Joseph E. Murray

- Performs the **first successful kidney transplant** -- between identical twins -- at the Peter Bent Brigham Hospital in **Boston**.
1967    Dr. Christiaan Barnard

- Performs the **first heart transplant** at Groote Shuur in Cape Town, South Africa.
Performs the first successful liver transplant.

Dr. Mohammad Taraz
Performs the **first successful lung transplant** at Toronto General Hospital.
1994: The FDA approves Prograf (marks a significant advance in the understanding & suppression of the human rejection response & in the lessening of unwanted side effects).

1995: CellCept & Neoral, a new formulation of cyclosporine, are approved by the FDA for use in transplant recipients.
Number of Transplants Performed in the USA 2000*

- Lung Transplant: 956
- Liver Transplant: 4,954
- Kidney Transplant: 13,327
- Kidney and Pancreas Transplant: 911
- Intestine Transplant: 79
- Heart Transplant: 2,198
- Heart and Lung Transplant: 48
- Pancreas Transplant: 435

In the year 2000, there were 5,984 cadaverous donors and 5,700 living donors that yielded usable organs.

*Source UNOS

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Patient Survival after Transplantation

- **Kidney**: 1y survival 97%, 5y survival 90%
- **Liver**: 1y survival 88%, 5y survival 77%
- **Heart**: 1y survival 90%, 5y survival 75%
- **Lung**: 1y survival 78%, 5y survival 49%

1y patient survival (%) vs. 5y patient survival (%)
But...

- Many more patients are in need of transplantation than there are organs available.

- In 2005, about 27,000 organ transplants were performed, whereas 90,000 people were waiting for organs.

- Consequently, a significant number of candidates die while waiting for a transplant.
Classification of grafts

- **Autograft**: Within an individual

- **Isograft**: Identical Twins

- **Allograft**: Non-identical

- **Xenograft**: Between species
Kidney Transplantation
All patients with ESRD are potential candidates for kidney transplantation unless contraindicated.
Absolute contraindications

- Current malignancy
- Active infection
- Active liver disease
- HBsAg-positive
- Severe or symptomatic cardiac or pulmonary disease
- Specific renal diseases with an accelerated recurrence rate
- Substance abuse
- Abnormal psychosocial & noncompliant behavior.
Relative contraindications

- Chronic liver disease
- Active infection
- HCV-positive
- HIV-positive
- Morbid obesity
- Current positive cross-match
- Age >70 years.
Stages of liver damage

Fatty Liver: Deposits of fat causes liver enlargement.
Liver Fibrosis: Scar tissue forms.
Cirrhosis: Growth of connective tissue destroys liver cells.
Indications for liver transplantation

- **Cholestatic liver disease** (Primary biliary cirrhosis and primary sclerosing cholangitis)
- **Hepatocellular liver disease** (Chronic viral hepatitis B or C, autoimmune, drug-induced, cryptogenic cirrhosis)
- **Vascular disease** (Budd-chiari)
- **Hepatic malignancy**
- **Inherited metabolic disorders**
- **Fulminant hepatic failure** (Viral hepatitis, Wilson's disease, drug or toxin induced).

**Controversial indications**
- **Alcohol-induced disease & some types of hepatic malignancies.** (recurrence of disease, as in the case of hepatic malignancies, or recidivism in the case of alcoholics)
Contraindications to Liver Transplantation

- Malignancy outside the liver
- Cholangiocarcinoma
- Active infection outside the biliary system
- Patients with alcoholic liver disease who continue to abuse alcohol
- Psychosocial instability & noncompliance
- Severe neurologic disease
- Advanced cardiopulmonary disease.

- HIV infection is not considered an absolute contraindication to transplantation.
Indications of Heart Transplantation

- NYHA functional class III or IV
- Having intolerable symptoms despite maximal medical & surgical management
- Lack of reversible factors
- A 1-year life expectancy of <50%.
New York Heart Association functional classification

**CLASS I**: No symptoms with ordinary physical activity

**CLASS II**: Some symptoms with ordinary activity and slight limitation of physical activity

**CLASS III**: Symptoms with less than ordinary activity and increased limitation of physical activity

**CLASS IV**: Symptoms with any activity, possibly even while at rest
Lung Transplantation
Indications of Lung Transplantation

- **COPD & idiopathic pulmonary fibrosis (IPF)** are the primary indications for a **single-lung transplant**.

- **Cystic fibrosis & $\alpha_1$-antitrypsin deficiency** are the primary indications for **bilateral lung transplant**.
In kidney transplantation, for the most part, native kidneys are not removed.
The transplanted liver is placed orthotopically; the recipient’s own liver must be removed.

Heart & Lung transplantation is usually an orthotopic procedure.
Transplantation Immunology
Successful organ transplantation has come from a greater understanding and application of pharmacology, microbiology, molecular & cellular biochemistry & biology, genetics, & immunology.

Suppression of the host's immune system & prevention of rejection are vital for host acceptance of the transplanted organ.

The ultimate goal is permanent acceptance or tolerance, a situation in which the new organ is seen as “self” by the host's immune system.

In general, the currently used immunosuppressive drugs provide a nonpermanent form of tolerance.
The degree to which allogeneic grafting is successful depends on the genetic similarities or differences between the organ of the donor & the immune system of the recipient.

The gene products encoded on the **HLA**:

- **Class I antigens** (**HLA-A**, **HLA-B**, & **HLA-C**) (present on all nucleated cell surfaces)
- **Class II antigens** (**HLA-DR**, **HLA-DQ**, **HLA-DP**) (found on macrophages, B cells, monocytes, activated T cells, dendritic cells, & some endothelial cells, all of which can act as APC)
- **Class III antigens** (**C4**, **C2**, & **Bf**) are part of the complement system & do not play a specific role in the graft rejection process.
Evaluation before Transplantation
- **Lymphocytes HLA Typing for HLA-A, HLA-B, & HLA-DR**
- **Panel Reactive Antibodies (PRA) test:**
  - The recipient's serum is tested against a cell panel of known HLA specificities that are representative of possible donors in the general population. The percentage of cell reactions (recipient with donor) determines a recipient's PRA.

- **Lymphocyte cross-match:**
  - The potential recipient's serum is cross-matched to determine whether preformed antibodies to the donor's lymphocytes are present. A positive cross-match indicates the presence of recipient cytotoxic IgG antibodies to the donor.

- **ABO blood typing**
  - Transplantation of an organ with ABO incompatibility would result in a hyperacute rejection & destruction of the graft.
Rejection of Transplantation
Pathophysiology of Rejection

The sequence of events that underlies graft rejection is:

- Recognition of the donor’s histocompatibility differences by the recipient’s immune system
- Recruitment of activated lymphocytes
- Initiation of immune effector mechanisms
- Finally graft destruction
Type of Rejections

- **Hyperacute Rejection**
  - May be evident within minutes of the transplantation procedure when preformed donor-specific antibodies are present in the recipient at the time of the transplant.

- **Acute Cellular Rejection**
  - Is most common in the first few months following transplantation but can occur at any time during the life of the allograft & generally is reversible within 1 to 3 days, if treated.

- **Acute Humoral Rejection**
  - Antibody-mediated process directed against HLA antigens present on the donor vascular endothelium.

- **Chronic Rejection**
  - A major cause of late graft loss & not reversible with any of the immunosuppressive agents currently available.
**General Approach To Treatment**

- **Induction Therapy**
  - Induction therapy involves the use of a high level of immunosuppression at the time of transplantation.

- **Maintenance Therapy**
  - The goal of maintenance immunosuppression is to prevent acute & chronic rejection while minimizing drug-related toxicity.
  - As patients progress through the post-transplant course, the risk of acute rejection ↓; thus allowing the clinician to gradually ↓ the doses of immunosuppressants or in some cases totally withdraw them over a period of 6 to 12 months in an effort to minimize adverse effects.
Immunosuppressive Drugs
Introduction

- **Short-term (i.e., 1–2-year) survival** after transplantation has improved dramatically. **Long-term survival** also has improved, but **not to the same degree**.

- Current immunosuppressive drug therapies are associated with **significant long-term complications**. These include **nephrotoxicity, hypertension, hyperlipidemia, osteoporosis, & diabetes**, as well as graft loss secondary to infection, malignancy, recurrence of primary disease, & nonadherence.

- **Although rates of acute rejection are significantly lower, this remains a problem, along with chronic rejection.**
Azathioprine
Azathioprine

- **AZA & 6-MP** are *purine antagonist* antimetabolites & is a *nonspecific* immunosuppressive agent, affects both cell-mediated (i.e., T cell) & antibody-mediated (i.e., B cell) immune responses.

- The introduction of CSA, TAC, MMF, & SIR has led to a **significant ↓ of AZA use** or its **elimination** altogether in immunosuppressive protocols, especially in the USA.

- Because it inhibits the **early stages** of cell differentiation & proliferation, AZA is useful for **preventing rejection**, but it is **ineffective for the treatment** of acute rejection.
Adverse Effects

- **Bone Marrow Suppression**: (most common adverse effect) presents as **leukopenia** or, less commonly, as **thrombocytopenia** & megaloblastic anemia.

- Myelosuppression is **dose dependent** & typically observed after 7 to 14 days of therapy.

- **Nausea & Vomiting**, which can be minimized by taking AZA with food.

- **Alopecia**, **hepatotoxicity** & **pancreatitis** are less-common adverse effects of AZA; they generally are reversible on dose reduction or discontinuation.
Drug Interactions

- **Allopurinol** inhibits xanthine oxidase & can ↑ the bioavailability of AZA & 6-MP concentrations by as much as 4-fold. (↑bone marrow suppression & pancytopenia)

- Doses of AZA should be ↓ by 50% to 75% when allopurinol is added.
Mycophenolate

- **Mycophenolic acid (MPA)** was first isolated from the *Penicillium glaucum* mold.

- **Mycophenolate mofetil** is the morpholinoethyl ester of MPA (both oral & IV formulations)

- **Mycophenolate sodium** is an enteric-coated formulation of the sodium salt of MPA (only oral formulation).

Gorgonzola an Italian cheese containing "veins" of *Penicillium glaucum*
MPA selectively, noncompetitively, & reversibly blocks an enzyme known as inosine monophosphate dehydrogenase (IMPDH) found primarily in actively proliferating T & B lymphocytes.

T & B lymphocytes rely on this enzyme & the de novo purine pathway to produce purine nucleotides for DNA & RNA synthesis. Thus, MPA interferes with T- & B-cell proliferation.
Mycophenolate mofetil
Adverse Effects of MMF

- **GI** (anorexia, nausea, vomiting & diarrhea, abdominal pain, gastritis) -- More common with higher dosages & occur with similar frequency during IV & oral therapy.

- **Hematologic** (leukopenia, thrombocytopenia, anemia)

- **Infectious**

- **If a patient complains from GI side effects:**
  - Try giving the dose without other medications
  - Administration with food
  - Giving smaller doses more frequently
  - lowering the dosage & titrating upward as tolerated
Mycophenolate sodium
The original **purpose** of designing the EC formulation was to **↓ or prevent** the GI side effects commonly seen with MMF.

All the compelling data currently published indicates, however, that the **efficacy rates & side effect profiles** of MMF & mycophenolate sodium are **nearly identical**.

**These 2 agents are not bioequivalent**; because a **1-g** dose of MMF is equivalent to **720 mg** of mycophenolate sodium.
Drug–Drug Interactions

- Administration with Al- & Mg-containing antacids or cholestyramine, significantly ↓ the AUC of MPA & should be avoided.

- It has been suggested that administration of iron may produce similar results, but this has not been tested.
Extracted from a soil fungus, *Tolypocladium inflatum* Gams.
Cyclosporine

- The introduction of CSA as an immunosuppressive agent has been the single most important factor in the current success of organ transplantation.

- In contrast to azathioprine & mycophenolate, cyclosporine has relatively nonmyelotoxic, immunosuppressive effects.

- Its use has ↑ patient & graft survival, ↓ morbidity associated with rejection & infection, & extended the types & numbers of organ transplantations performed.
Neoral vs. Sandimmune

- Modified cyclosporine (Neoral), a readily absorbed cyclosporine formulation in a solubilized microemulsified state.

- Neoral's bioavailability is better than that of Sandimmune, so less intrapatient & interpatient variability is seen in transplant recipients.

- The microemulsion formulation is self-emulsifying & forms a microemulsion spontaneously with aqueous fluids in the GI tract, making it less dependent on bile for absorption.

- Neoral & Sandimmune are not bioequivalent & therefore, not interchangeable.
Adverse Effects of CSA

- **Nephrotoxicity** (often related to the dose & duration of exposure) (NSAIDs)
- **Hypertension/ Hyperlipidemia**
- **Neurotoxicity** (Tremors, Headaches, Seizures, Paresthesias)
- **Hypomagnesemia/ Hypo- or hyperkalemia**
- **Hyperuricemia, Hyperglycemia, gout**
- **Cosmetic changes (Gingival hyperplasia, Hirsutism)**
- **Hepatotoxicity**
Drug–Drug Interactions

- Drug interactions occur frequently with the CNIs because they are substrates for CYP3A4 & P-glycoprotein.

- Some centers take advantage of these interactions by routinely prescribing CYP3A4 inhibitors to ↓ the dosage & cost of CNI therapy while maintaining the same therapeutic concentrations.

- Grapefruit juice (potent inhibitors of CYP3A4) ↑ CSA concentrations significantly.
Drug–Drug Interactions

- CSA & to a lesser extent, TAC are inhibitors of CYP3A4. The inhibitory effects of TAC & CSA on CYP3A4 can be seen with weaker substrates, such as the Statins.

- Concomitant administration of a CNI with an Statin results in an ↑ in the Statin levels, which ↑ the risk of Statin adverse effects, most notably myopathy.

- Patients should be monitored for clinical signs of myopathy when receiving Statins in combination with CSA & TAC.

- Consistency in administration of the CNIs with regard to meals & food intake is important to sustain an effective concentration time profile. High-fat meals can enhance both plasma clearance & the volume of distribution of CSA by more than 60%.
Proportion of Drugs Metabolized by CYP450 Isozymes

- CYP3A4/5: 36%
- CYP2D6: 19%
- CYP2C8/9: 16%
- CYP1A2: 11%
- CYP2C19: 8%
- CYP2E1: 4%
- CYP2B6: 3%
- CYP2A6: 3%
Tacrolimus (formerly FK506)

- Is isolated from a soil fungus, *Streptomyces tsukubaensis*.
Tacrolimus

- Predominantly metabolized in the liver through the CYP 3A4 & is primarily eliminated from the body as several inactive metabolites.

- Varying degrees of liver dysfunction, including cirrhosis & severe cholestasis, may have dramatic effects on the metabolism & excretion of TAC.

- Oral TAC should be administered on an empty stomach or taken consistently in relation to meals.

- Most institutions extemporaneously prepare an oral solution for NG tube administration because it is not commercially available.
Adverse Drug Reactions

- **Nephrotoxicity**
- **Major neurologic toxicities** (confusion, seizures, dysarthria, persistent coma)
- **Minor neurologic toxicities** (tremors, **headache**, & sleep disturbances)
- **Hypertension**
- **Diarrhea, nausea, vomiting & anorexia**, hypomagnesemia, hyperkalemia, hemolytic anemia, hemolytic uremic syndrome, **alopecia**, ↑susceptibility to infection & malignancy.
- **Hyperglycemia**
Tacrolimus vs. Cyclosporine

- TAC may be associated with a ↑ occurrence of neurologic complications compared to CSA.
- CSA appears to have a greater propensity to cause or worsen HTN & hyperlipidemia compared to TAC.
- Hyperglycemia is more common with TAC than CSA, but is often reversible when doses of TAC&/or corticosteroids are ↓.

- CSA is associated with cosmetic changes, such as hirsutism & gingival hyperplasia, which may be managed by converting from CSA to TAC or by proper hygiene in patients who cannot be switched to TAC.

- TAC, in contrast, has been reported to cause alopecia, which is usually self-limiting & reversible.
Sirolimus (Rapamune)®

- **Mammalian Target Of Rapamycin Inhibitors**
- It was isolated from soil samples (*Streptomyces hygroscopicus*) in Rapa Nui (Easter Island) & is a macrolide, structurally related to TAC.
- Also known as rapamycin.
Everolimus

Mammalian Target Of Rapamycin Inhibitors
Adverse Effects

- **Myelosuppression** *(Thrombocytopenia/ leukopenia /anemia) *(Transient)*
- **Hypercholesterolemia & hypertriglyceridemia** *(quite common/ dose-related)*
- **Delayed wound healing & dehiscence**
- **Mouth ulcers**
- **Reversible interstitial pneumonitis**
- **↑ liver enzymes, HTN, rash, Acne, Diarrhea & Arthralgia, nausea & vomiting, hypokalemia, infection.**
- **Proteinuria in renal transplant recipients**
Drug–Drug Interactions

- The major metabolic pathway for sirolimus is CYP3A4.
- As with CSA & TAC, grapefruit juice ↑ sirolimus levels.
Corticosteroids

- Prednisone, methylprednisolone, & prednisolone—all synthetic analogs of hydrocortisone—are the primary corticosteroids used to prevent & treat rejection of transplanted organs.

- Although an important part of immunosuppression, a goal of most transplantation programs, is to minimize, eliminate, or avoid corticosteroid use because of their numerous & significant side effects.
Therapeutic Drug Monitoring

Dr. Mohammad Taraz
- Cyclosporine
- Sirolimus
- Tacrolimus

Monitoring MPA serum concentrations is controversial & not generally recommended at this time because of so much intrapatient & interpatient PK variability.
Polyclonal Antibodies *(Antithymocyte Globulins)*

- Equine globulin (Atgam)
- Rabbit globulin (Thymoglobulin)

Monoclonal antibodies

- IL-2 Receptor Antagonists
  - Basiliximab
  - Daclizumab
- Muromonab-CD3
Production of Monoclonal Antibodies

1. Culture in HAT medium
2. Test each supernatant for antibodies
3. Clone each positive culture
4. Test each supernatant for antibodies
5. Expand positive clones

Propagate

Harvest monoclonal antibodies

in vitro

or

in vivo
Production of Polyclonal Antibodies

- injection of **homogenized human spleen or thymus preparations** into the animals. This injection induces an immune response in the animals directed against human T lymphocytes; serum containing **antibodies to T cells** is collected from the animals & purified.

- **Other antibodies to human cells are produced as well, however.** These antibodies **bind to all normal blood mononuclear cells in addition to T lymphocytes & B lymphocytes**, resulting in depletion of lymphocytes, platelets, & leukocytes from the peripheral circulation.
Atgam

- Effective as **induction therapy** or as **treatment of acute rejection**.

- Dose is 10 to 20 mg/kg/day.

- Usually infused into a **high-flow central vein** to ↓ pain, erythema, & phlebitis at the injection site.
Thymoglobulin

- Effective as *induction therapy* or as treatment of acute rejection.

- Dose is 1.5 mg/kg/day.

- Usually infused into a **high-flow central vein** to ↓ pain, erythema, & phlebitis at the injection site.
Thymoglobulin® vs. Atgam®

- Thymoglobulin appears to be more effective than Atgam & consider as the polyclonal antibody of choice.

- Skin testing is recommended before horse-derived antithymocyte globulin use, but not rabbit-derived Thymoglobulin. (The rabbit preparation is less immunogenic.)
Adverse Effects of ATG & RATG

- Most adverse effects reported with ATG & RATG are related to the lack of specificity for T cells owing to their polyclonal nature.

- Dose-limiting myelosuppression (leukopenia, anemia, & thrombocytopenia).

- Infusion-related febrile reactions (premedication with acetaminophen, diphenhydramine, & corticosteroids)

- ↑ risk of infections (particularly viral infections)

- ↑ risk of malignancy
IL-2 Receptor Antagonists
IL-2 Receptor Antagonists

- **Basiliximab**, chimeric monoclonal antibody
  (75% human, 25% murine)

- **Daclizumab**, humanized monoclonal antibody
  (90% human, 10% murine)
Monoclonal Antibody

Chimeric

Mouse variable region

Human constant region (Fc)

Humanised

Human regions

Mouse antigen-binding sequences

Human constant region (Fc)
Daclizumab

- Approved for use in combination with other immunosuppressives to prevent acute cellular rejection in kidney transplantation. (not considered treatment for acute rejection)

- Given as 1 mg/kg on day 0 of the transplant & then every 2 weeks for 4 more doses.

- Terminal half-life of 11 to 38 days.

- Using the approved 5-dose regimen, saturates the IL-2R for about 120 days.
Basiliximab

- Approved for use in combination with other immunosuppressives to prevent acute cellular rejection in kidney transplantation. (not considered treatment for acute rejection)

- Given as a 20-mg dose on days 0 & 4 after transplantation.
- Terminal half-life of 4 to 14 days.
- With the 2-dose regimen, saturates the receptor for 36 days.
Orthoclone OKT3®
Muromonab-CD3 (Orthoclone OKT3®)

- Murine monoclonal antibody to the CD3 receptor on mature human T cells.

- Minutes following the administration of OKT3, T-cell concentrations ↓ dramatically.

- It is used for induction therapy (prophylaxis) or to treat acute graft rejection.
Adverse Effects of OKT3

- OKT3 administration is associated with **significant first-dose adverse reactions**.

- **Cytokine-release syndrome** (fever, chills, rigors, pruritus, & alterations in BP) may occur with the first several doses.

- **Premedications** with Methylprednisolone, Acetaminophen, Diphenhydramine, Indomethacin, & Pentoxifylline.
Alemtuzumab
Alemtuzumab

- **Humanized** monoclonal antibody directed at cells that express the **CD52 surface antigen**, which is found on both **T & B cells**, as well as macrophages, monocytes, eosinophils, & natural killer cells.

- When binds to the CD52 surface antigen, antibody-dependent lysis occurs, which removes both T & B lymphocytes from the blood, bone marrow, & organs, resulting in **complete lymphocyte depletion**.

- Approved for use in B-cell chronic lymphocytic **leukemia**. However, its effects on depleting both T & B lymphocytes **make it useful in solid-organ transplants**.
Investigational Agents

- **Belatacept** blocks the costimulatory pathway of CD28 or CTL-A4: CD80/CD86 binding interactions.
- **Leflunomide** target pyrimidine synthesis.
- **Mizoribine & brequinar** are inhibitors of DNA synthesis.
- **Deoxyspergualin** inhibits cell activation & maturation.
Immunosuppressant-related Complications

- **Hypertension**
  - Corticosteroids, cyclosporine, tacrolimus, & impaired kidney graft function

- **Hyperlipidemia**
  - May be exacerbated by corticosteroids, CNIs, sirolimus, diuretics, & β-blockers

- **Post-Transplantation Diabetes Mellitus**
  - Corticosteroids & CNIs
Immunosuppressant-related Complications

- **Post-Transplantation Osteoporosis**
  - Corticosteroids, cyclosporine loop diuretics, or Al-containing phosphate binders

- **Infection**
  - CMV is the most important viral pathogen affecting transplant patients

- **Malignancy**
  - Post-transplantation lymphomas & lymphoproliferative disorders (PTLD), Kaposi sarcoma, renal carcinoma, in situ carcinomas of the uterine cervix, hepatobiliary tumors, & anogenital carcinomas.

- Skin cancers are the most common tumors, accounting for 38% of all malignancies.
Duration of immunosuppressive drugs treatment

- After the initial transplantation period, drug dosages are ↓ over time & maintained at a stable dose for 6 months to 1 year.

- Although the discontinuation of a drug may ↓ adverse effects, it must be counterbalanced against the risk of acute rejection & graft loss.

- Monotherapy, generally with TAC or CSA, may be achieved in kidney, liver, & heart transplant recipients at some point after transplantation.

- Most patients, however, require lifetime immunosuppression.
Pharmacist
Patient Education
Drug-Drug Interactions
Side effect of drugs
Duration of treatment & it’s obligation