Solid Organ Transplantation
Transplantation

- Solid organ transplantation
- Bone marrow transplantation (BMT)
Introduction

• Solid-organ transplantation provides a lifesaving treatment for patients with end-stage cardiac, kidney, liver, lung, and intestinal disease.

• Kidney transplants remain the most common

• The next most frequently transplanted organs were liver, heart, pancreas (or combined kidney–pancreas) and lung transplants in US.

• While the demand for transplantation continues to grow, the number of cadaveric donors has remained relatively stable during the last decade

• To increase the number of organs available for transplantation: The use of living donors for renal transplantation represents over one third of all kidney transplants, more than any other organ.
Introduction

• Efforts to expand the cadaveric donor pool: relaxation of age restrictions, development of better preservation solutions, use of “extended-criteria” and non–heart-beating donors, and, in the case of liver transplants, the transplantation of one liver to more than one recipient or implantation of only a segment of a liver.

• Strategies to increase the living donor pool include using plasmapheresis before transplant to remove antibodies to allow for transplanting organs that are not ABO-compatible with the recipient or organs into recipients with donor-specific antibodies.

• Dialysis, Left ventricular assist devices but liver?
Kidney

• Renal transplantation is the preferred long-term therapeutic option for most patients with ESRD because it provides patients with the greatest potential improvement in quality of life:
  • Dialysis catheter-related infections, peritoneal dialysis-associated peritonitis, and scheduled dialysis treatments are avoided, and dietary restrictions are fewer
Major Histocompatibility Complex
Human Leukocyte Antigen (HLA)

• The degree to which allogenic grafting is successful depends on **genetic similarities or differences** between the donor’s organ and the **immune system** of the recipient.

• Rejection is the outcome of the natural response of the immune system to a foreign substance.

• The closer HLA matching between donor and recipient, the better the outcome particularly over the long-term.
Tissue typing

- **Lymphocytes** are typed for HLA-A, HLA-B, HLA-DR (HLA-typing or Haplotyping)

- Lymphocyte **cross-match** to determine whether preformed Ab to the donor’s lymphocytes are present in recipient’s serum.
Tissue typing

- **PRAs**: to assess organ compatibility because recipients may have HLA antibodies from previous exposure to antigenic stimuli (e.g. blood transfusions, previous transplantation, pregnancy)
  - In this test, recipient serum is tested against a cell panel of known HLA specificities that are representative of possible donor in the general population
  - PRA > 20% to > 50% shows high risk for rejection

- **ABO blood typing**

What is differences between various organ transplantations?
Kidney Transplantation

• **Absolute contraindications:**
  - Active infections
  - Active malignancy
  - Active substance abuse
  - Reversible renal failure
  - Uncontrolled psychiatric disease
  - Documented active and ongoing treatment non-adherence
  - A significantly shortened life expectancy
Relative contraindications

- Malnutrition, primary oxalosis
- Active systemic diseases that may have caused kidney failure (such as ANCA-associated vasculitides or SLE), severe hyperparathyroidism
- CVD
  - Patients with known heart disease, or who are at high risk for heart disease, are eligible for transplantation but require careful evaluation
- Infection
  - HIV, CMV, EBV, and hepatitis B and C virus
- GI disease
  - Peptic ulcer disease, cholelithiasis, and diseases of the colon and liver
Relative contraindications

- **Cerebrovascular disease**: Older patients with risk factors such as HTN, cigarette smoking, and hypercholesterolemia should be carefully examined for evidence of carotid stenosis, which should be evaluated and addressed prior to transplantation.
- **Peripheral vascular disease**: Bilateral femoral and pedal pulses should be carefully assessed in every transplant candidate, particularly those with diabetes, CVD, or history of PVD.
- **Pulmonary disease**
- **Malignancy**: It is important to screen for malignancy prior to transplantation.
Relative contraindications

- Patients with a history of cancer: waiting period free of recurrence of two to five years for most patients with a history of carcinoma
- Abnormal lower urinary tract
- Hematologic disorders
- Obesity
- Psychosocial issues
- Frailty
- Renal diagnosis
Stages of CD4 T-cell activation and cytokine production with identification of the sites of action of different immunosuppressive agents.
Induction Therapy

- For pancreas, heart, lung transplant
- For high risk patients in kidney transplantation
- Some consider more potent agents (OKT3, ATG) for high-risk patients and IL-2 receptor Ab for low- to intermediate-risk patients
Antithymocyte Globulin

- Antilymphocyte globulin (ATG)
- They are polyclonal antibodies produced by injection of human spleen or thymus to animals that induce their immune response against human T-lymphocytes
  - Equine (Atgam®, lymphoglobulin®); Inj 100 mg/5 mL, 250 mg/5 mL
  - Rabbit (Thymoglobulin®);
    - Genzyme; powder for inj 25 mg
Antithymocyte Globulin

• Unfortunately, Ab to other human cells may produce

• These Ab bind to all normal blood mononuclear cells in addition to T or B cells and result in depletion of lymphocytes, plts, leukocytes.
Antithymocyte Globulin

• Rabit form is more effective than Horse form

• Thymoglobulin: 1.5 mg/kg/d; high dose 3-6 mg/kg; Genzyme and Fresenious are not equivalent.

• Antithymocyte globulin: 10-20 mg/kg/d.
Antithymocyte Globulin

- Dilute in NS
- Administer over 4-6 in high-flow central vein to reduce pain, erythema, phlebitis at injection site
- 3-10 days for induction
- 7-14 days to Tx acute rejection

ADRs:
- Fever, chills, N/V due to cytokine release; can be minimized by premedication with acetaminophen & diphenhydramine before each dose.
Antithymocyte Globulin

- Erythema, rash, pruritus, H/A, leukopenia, thrombocytopenia are common

- Serum sickness leading to acute glomerulonephritis, hypotension, ARDS; sometimes between 1 week of therapy to 2 weeks of drug D/C.

Delayed ADRs:
- ↑ viral and bacterial opportunistic infections
Antithymocyte Globulin

**Monitoring:**

- VS hourly during infusion

- WBC, plt daily (WBC < 3000 or plt < 100,000 reduce dose by 50% or hold to counts return to desired level)
IL-2 Receptor Antagonist

- Basiliximab (Simulect) (higher amounts of murine Ab)
- Powder for Inj 10 mg, 20 mg
- Monoclonal Ab
- **Bind to IL-2R** and prevent the binding of IL-2 to IL-2R, thereby blocking T-cell activation.
- Induction agent
- Reduce acute rejection episodes in kidney transplant
IL-2 Receptor Antagonist

Advantages to older agents:

• Ease of administration (bolus or IV infusion over 20-30 min)
• Minimal side effects
• Low immunogenicity
• No greater infection rates
• No greater malignancy rates
• Fewer required doses (20 mg within 2 hours prior to transplant surgery followed by a second 20 mg dose 4 days after transplantation)
Kidney Transplantation

- 1 g MMF, PO before transplant
- 1 g cefazolin, IV before transplant
- 500 mg methylprednisolone during surgery
- 100 mg furosemide after the kidney has been transplanted
- 250 mg methylprednisolone, the day after surgery
- 100 mg methylprednisolone, the second day after surgery
- 1 mg/kg prednisolone, the third day after surgery Then taper 0.3 mg/kg/day to 20 mg/d
Kidney Transplantation

- Cyclosporine 6 mg/kg/d, 12 h after transplant
- MMF 1 g, PO, BD
- Cefazolin 1 g, Q 8 h, for 2 doses after surgery
- Ranitidine
- Nystatin
- Sliding Scale regular Ins
Kidney Transplantation

- CNIs + MMF/Sirolimus/AZA + Prednisolone ± monoclonal or polyclonal Abs
  - Steroid withdrawal
  - CNIs withdrawal
Calcineurin inhibitors

Cyclosporine
Tacrolimus

- Inhibit interleukin (IL)-2 and thus block T-cell activation

- Has no effect on hematopoietic cells (non-myelotoxic) or neutrophils
Cyclosporine

- **Sandimmune®, Neoral®, Imminoral®**
- **Cap 25, 50, 100 mg; oral solution 100 mg/mL, injection solution 50 mg/mL (1.5 mL); ophthalmic solution 0.05%**

- **Neoral has:**
  - Shorter $T_{\text{max}}$
  - Higher $C_{\text{max}}$
  - Greater AUC

- **Renal:** $9 \pm 3$ mg/kg daily, in 2 divided doses
Cyclosporine

- To avoid high $C_{\text{max}}$ and maintain adequate $C_{\text{trough}}$, TDS dosing may be required.

If no desired level consider:
- inappropriate drug administration
- altered GI function
- noncompliance
- assay error
- poor absorption of dosage form, drug interactions
Cyclosporine ADRs:

- Nephrotoxicity
- Neurotoxicity (tremors, H/A, seizure, paresthesia)
- HTN (CCB)
- Hypomagnesemia
- Hyper/hypokalemia
- Hyperuricemia, gout
- Hemolytic anemia
- Cosmetic (hirsutism, gingival hyperplasia)
- ↑ Risk of infection and malignancy
- Hyperglycemia
- Hepatotoxicity
Tacrolimus (Prograf®)

- FK506
- Similar to cyclosporine
- Cograft®
- Cap 0.5, 1, 5 mg;
- Inj Sol 5 mg/1 mL
- Kidney transplant: 0.1 mg/kg/day in combination with mycophenolate mofetil; titrate to target trough concentrations. Administer in 2 divided doses, given every 12 hours.
Tacrolimus

- Avoid IV use because of more N/V, H/A, and other neurotoxicity and nephrotoxicity and anaphylaxis

- Take on an empty stomach or taken consistently in relation to meal

- Consider at least 24 h interval between initiating Tac after cyclosporine D/C.
Tacrolimus ADRs:

- Nephrotoxicity
- Major neurotoxicity (confusion, seizure, dysarthria, persistent coma)
- Minor neurotoxicity (tremors, H/A, sleep disturbances)
- HTN
- D, N/V, anorexia
- Hypomagnesaemia
- Hyperkalemia
- Hemolytic anemia
- Alopecia; no gingival hyperplasia (in contrast to cyclosporine)
- ↑ Risk of infection and malignancy
- Hyperglycemia
Corticosteroids

• Their anti-inflammatory and immunosuppressive properties are the basis of their role in organ transplantation

• Prednisolone tab 5, 50 mg

• Methylprednisolone (Solumedrol®) 500 mg
Azathioprine (Imuran®)

- Tab 50 mg, Injection powder 50 mg
- Prodrug of 6-MP (Tab 50 mg)
- Purine antagonist antimetabolites

- A non-specific immunosuppressive agent affect both cell mediated (T-cell) and humoral mediated (B-cell) immune response.
Azathioprine

- For prevention of acute rejection
- Ineffective for Tx of acute rejection
Azathioprine ADRs

BMS:

- Leukopenia, and less commonly Thrombocytopenia, and Megaloblastic anemia

- BMS is dose dependent
Azathioprine other ADRs

- Hepatitis
- Cholestasis
- Reversible and irreversible liver damage
- D/C AZA if hepatotoxicity or other serious ADR occurred.
- Pancreatitis
- Long term administration has been associated with post transplant malignancy.
Mycophenolate Mofetil (Cellcept®)

- Cap 250 mg, Tab 500 mg
- Mycophenolate sodium (Myfortic®): EC tab 180, 360 mg
- Has replaced AZA in many transplantation protocols
- As rescue therapy when pts have not responded to or can not tolerate the ADRs of other immunosuppressive agents.
MMF

• Interferes with T- and B-cell proliferation and activity

ADRs:
• GI (anorexia, N/V, D, gastritis); smaller dose, more frequently
• Hematologic (leukopenia, thrombocytopenia, anemia);
  • WBC < 3000 or ANC < 1500 reduce dose or D/C MMF
• Infection
Sirolimus

- Rapamycin (Rapamune®)
- Tab 1, 5 mg
- The proliferation signal inhibitors (PSI) sirolimus and everolimus exert their activity by inhibiting the mechanistic target of rapamycin (mTOR) receptor, which alters T-cell response to IL-2.
- Sirolimus may reduce the development of chronic rejection.
- It is contraindicated in the early liver or lung transplantation.
- Initial LD (6 mg) then, once daily MD (2 mg).
- Administer 4 h after cyclosporine morning dose.
Sirolimus

**ADRs:**
- Oral ulceration
- Impaired wound healing
- N/V/D
- Arthralgia
- Epistaxis
- Rash, acne
- Leukopenia, thrombocytopenia, anemia (in contrast to CNIs)
- HTN
- Hypokalemia
- HyperTG (more than CNIs)
Comparison of Common Adverse Effects of Maintenance Immunosuppressants

<table>
<thead>
<tr>
<th>AZA</th>
<th>MMF</th>
<th>SIR/EVR</th>
<th>Steroids</th>
<th>CSA</th>
<th>TAC</th>
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</thead>
<tbody>
<tr>
<td>Nausea, vomiting</td>
<td>Diarrhea, nausea</td>
<td>Hyperlipidemia</td>
<td>GI bleeding, Hyperlipidemia, Leukocytosis</td>
<td>Hyperlipidemia, Nephrotoxicity, Tremor, Hypertension</td>
<td>Diarrhea, nausea, Hepatotoxicity, Nephrotoxicity, Tremor, headache, Hypertension</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
<td>Hyperlipidemia, Leukopenia</td>
<td>Hyperglycemia, Gingival hyperplasia</td>
<td>Hyperglycemia, Hyperkalemia, hypomagnesemia</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
<td>Hyperlipidemia</td>
<td>Weight gain, Hypertension, Hypertension</td>
<td>Hirsutism</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mood changes</td>
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</table>
Delayed graft function (DGF)

- The need for dialysis in the first postop week or the failure of the serum creatinine to fall by 30% of the pretransplantation value.
- The primary cause of DGF is ATN
  - donors who recently experienced a cardiac arrest, those who were hypotensive or on vasopressors, or older donors (age >55 years).
  - While cyclosporine and tacrolimus have been implicated in the prolongation of ATN, a clear cause-and-effect relationship has not been established.
- DGF predisposes patients to acute rejection, possibly as a consequence of decreased CNI levels and a resultant reduction in the level of immunosuppression.
Rejection in all solid organ transplantation

- Hyperacute
- Accelerated
- Acute
- Chronic
Hyper-acute rejection

- Occurs within minutes to hours after transplantation and is the result of preformed cytotoxic against donor MHC class I Ags

- Is rare because of ABO and HLA matching (MHC class 1)

- Pt presents with anuria, hyperkalemia, HTN, metabolic acidosis, pulmonary edema, and sometimes DIC

- Remove transplanted kidney
Accelerated rejection

- **Within 2-6 days** after organ transplantation
- **Due to prior sensitization** to Ags similar to those of the donor and newly developed donor-specific Abs

- **Most in pts with:**
  1. prior transplantation
  2. multiple pregnancies
  3. multiple blood transfusions

- Have good renal function prior to AKI
- Generally are more resistant to pharmacologic therapy
Acute rejection

- Most common type of rejection
- The **only** type of rejection that respond to therapy
- **Reduce survival** of living and cadaveric transplant
- May occur in the first *5-10 days* after transplant
- **Induction** may delay it for several weeks
- Usually **within first year of transplant** (most within first 2 mo)
Acute rejection

- Methylprednisolone 500 mg/d × 3 days → first choice for mild to moderate acute rejection

- IV ATG for steroid resistant acute rejection or for severe acute rejection

- OKT3 and Alemtuzumab
# Differential Diagnosis of Acute Rejection and Cyclosporine or Tacrolimus Nephrotoxicity

<table>
<thead>
<tr>
<th>Nephrotoxicity in Renal Transplant Recipients</th>
<th>Acute Rejection</th>
<th>CSA or TAC Nephrotoxicity</th>
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<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often &lt;4 weeks postoperatively</td>
<td></td>
<td>Often &gt;6 weeks postoperatively</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>Afebrile</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td>Graft nontender</td>
</tr>
<tr>
<td>Graft swelling/tenderness</td>
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<td>Good urine output</td>
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<tr>
<td>Decreased daily urine volume</td>
<td></td>
<td></td>
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<tr>
<td><strong>Laboratory biopsy</strong></td>
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<tr>
<td>Rapid rise in serum Cr (0.3 mg/dL/day [27 μmol/L/day])</td>
<td></td>
<td>Gradual rise in serum Cr (&gt;0.15 mg/dL/day [&gt;13 μmol/L/day])</td>
</tr>
<tr>
<td>Normal CSA or TAC concentration</td>
<td></td>
<td>Elevated CSA or TAC concentration</td>
</tr>
<tr>
<td>Interstitial lymphocytic infiltrates</td>
<td></td>
<td>Interstitial fibrosis, tubular atrophy, glomerular thrombosis, arterial inflammation</td>
</tr>
</tbody>
</table>

Cr, creatinine; CSA, cyclosporine; TAC, tacrolimus.
Chronic Rejection

- Usually after 1y in 30-40% of pts
- HTN, proteinuria, progressive decline in renal function ⇒ RF
- **Immunologic factors** that ↑chronic rejection:
  - History of acute rejection
  - Inadequate immunosuppression
  - Non-compliance with immunosuppression
  - Previous infection, e.g. CMV
Chronic Rejection

- **Non-immunologic factors** that ↑ chronic rejection:
  - Donor related (Age, HTN, DM)
  - ↑ Ischemic time
  - Recipient (HTN, hyperlipidemia)
  - CNI nephrotoxicity
  - ↑ BMI
Chronic Rejection

• IVIG & Rituximab

• Irreversible

• Unaffected by ↑immunosuppressive therapy

• Need dialysis, re-transplantation
Drug Interactions

• Drug-Drug interactions
• Drug-Disease
• Drug-Herb (Hypericum, Echinacea, Silymarin)
• Drug-Food/beverage (grapefruit juice)
• Drug-smoking
• Drug-Wallet
Initiation and Management of Drug Therapy

Therapeutic objective
(prevention of rejection)

Choose drug & dosing regimen

Monitor therapeutic and toxic response

PK

PD
Drug Interactions

**Pharmacokinetic drug interactions** *(Substance A affects the absorption, distribution, metabolism, or excretion of substance B)*

**Pharmacodynamic drug interactions**

Substance A enhances or antagonizes the intended effect of substance B

**Additive Toxicity**

Substance A enhances the adverse effects of substance B
Pharmacokinetic Drug-Drug Interactions

Absorption:

Only drugs which alter the extent, but not the rate of immunosuppressive absorption are clinically important.

Food decreases the rate not extent of MMF absorption

Food significantly reduces the rate and extent of tacrolimus absorption.

Tacrolimus should be taken on an empty stomach to increase oral absorption.

GI absorption of cyclosporine and tacrolimus can be affected by adding a prokinetic agent.
Pharmacokinetic Drug-Drug Interactions

- Absorption:
  - Product A binds with product B in the GI tract (CNIs, Sir, MMF)
    - Cholestyramine, colestipol, sevelamer
  - Most common example is chelation of agents with di/trivalent metals
    - E.g. Mg, antacids
      - chelate MMF
  - Result = decreased effectiveness of both
  - Management = separate doses (**2 hour before or 4 hours after**)

Orlistat significantly ↓ the absorption of Cyclosporine, administer 3 hours before cyclosporine
Pharmacokinetic Drug-Drug Interactions

Distribution
- Least common type of pharmacokinetic interaction

Metabolism
- Most common type of PK drug interaction
  1. Cytochrome P-450 isoenzymes
  2. P-glycoprotein transport
Cytochrome P450

Cyt P450

P450 I
A2
D6
P450 II
C9
C19

P450 III
A4
A5
Pharmacokinetic Drug-Drug Interactions

Hepatic enzymes – **Cytochrome P450 system** metabolizes numerous drugs

- Many different isoenzymes
  - 3A4, 2D6, 1A2, 2C9, and 2C19 most common
  - 3A4 most clinically significant
- Many drugs **induce** or **inhibit** certain hepatic enzymes
- Many drugs are **substrates** of the Cyt. P450 system
Proportion of Drugs Metabolized by Cyt. P450 Isozymes

- CYP3A4: 36%
- CYP2D6: 19%
- CYP2C19
- CYP2C9
- CYP2E1
- CYP2B6
- CYP2A6
- CYP1A2
Pharmacokinetic Drug-Drug Interactions

• **Metabolism**
  - Drugs that *induce* this system *decrease* the concentrations of other drugs metabolized by Cyt. P450 (results in decreased therapeutic effects)
  - Drugs that *inhibit* Cyt. P450 enzymes cause *increases* in the concentrations of other drugs metabolized by Cyt. P450 (may increase risk of adverse effects)
P-Glycoprotein Transport

- Trans-membrane efflux pump
- Tumor cell overexpression → chemotherapy resistance
- Intestinal site → reduced drug absorption
- BBB prevents CSF distribution
- Proximal tubular epithelium → increased urinary excretion
P-Glycoprotein & Cyt. P450 3A4

- Co-localize to liver and intestine
- Decrease intracellular drug concentrations
- High degree of shared substrate
  - CCBs, antifungal azoles, immunosuppressives, macrolides
Inhibitors of Cyt. P450
(Interaction with CNIs, Sir)

- Increase concentration, effects, and toxicities of Cyc, Tac, Sir
- **Macrolides** (erythromycin, clarithromycin)
- **Azole antifungal agents** (Keto, Itra, Fluc, Vori)
- **SSRIs** (fluo, fluvox, citalopram)
- **Other antidepressants** (nefazodone)
Inhibitors of Cyt. P450
(Interaction with CNIs, Sir)

- **CCBs** (diltiazem, verapamil)
- **PIs** (indinavir, nelfinavir, ritonavir, saqui, ampre)
- **NNRTIs** (dalavirdine)
- **H₂-blockers** (cimetidine)
- Amiodarone
- Grapefruit
- Chloramphenicol
Antidepressants

• Many Cyt. P450 interactions possible
• Relative ranking of newer antidepressants based on Cyt. P450 drug interaction potential:
  • Most likely to interact:
    • Fluvoxamine, fluoxetine, paroxetine, nefazodone
  • Less likely to interact
    • Sertraline
  • Least likely to interact
    • Mirtazapine, venlafaxine, citalopram
Inhibitors of Cyt. P450

• Cyc & Tac inhibit Cyt. P450 3A4 and increase concentration and toxicities of Statins

• Rhabdomyolysis
Common, Clinically Significant Drug Interactions: Statins

- Avoid Lovastatin

- Lower dose of other statins

- Note that pravastatin has fewer Cyt. P450 3A4 interactions and may be preferable statin.

- Fluvastatin, Rosuvastatin
Inducers of Cyt. P450 (Interaction with CNIs, Sir)

- **Anticonvulsants** (CBMZ, Phenobarb, Phenytoin)
- **Rifampin**
- **NNRTIs** (Efavirenz, Nevirapine)
- **St. John's wort** (Hypericum)
Other Metabolizing Enzymes Interactions

- AZA + Allopurinol
Mycophenolate Mofetil

- Tacrolimus inhibits MMF metabolism ⇒ significant increase in mycophenolic acid drug concentrations

**Management:**
- monitor for increased MMF side effects
Pharmacodynamic drug interactions

- ACEIs & CNIs → Hyperkalemia
- MMF & Metoclopramide → Diarrhea
- Echinacea
- AGs, Van, Cipro (additive nephrotoxicity)
- Cipro, Imipenem (additive neurotoxicity)
- Phenytoin (gingival hyperplasia)
- Minoxidil (hirsutism)
Post-transplant Cardiovascular Disease

- CV disease is the **major cause of death** among kidney transplant pts
- CV disease is the major cause of morbidity in all organ transplant recipients
- Many kidney transplant pts had CV disease (HTN, hyperlipidemia, LVH, peripheral vascular disease, IHD) before transplant
- HyperHcy, smoking, age, obesity, DM, family history/immunosuppressive drugs may have roles
Post-transplant HTN

- Prevalence of 40-100% in all solid organ transplant
- More prevalent in kidney and heart transplant
- Prevalence increase with time after transplant
- Have negative impact on graft and pt survival
- More prevalent in men
- Immunosuppressives have role
Cyclosporine-induced HTN

- Dose dependent
- The prevalence of HTN is lower with Tacrolimus
- Corticosteroid also has role in HTN
- Antihypertensive drugs besides diet + lifestyle, If SBP > 140 or DBP > 90
Cyclosporine-induced HTN

• Traditionally, **CCBs** have been considered the choice due to their preferential effect on afferent arterioles

• Diltiazem, verapamil, nicardipine and possibly amlodipine but not nifedipine, isradipine, felodipine, nitrendipine $\Rightarrow \uparrow$[CNI]

• **ACEIs or ABS** may be used especially if HF, proteinuria, DM

• Other antihypertensive drugs also may be used
Cyclosporine-induced Hyperlipidemia

- In 30-80% of transplant pts
- ↑Total-C, ↑LDL-C, ↑TG, ↑HDL-C often seen within 3-6 mo and later after transplant
- More common in kidney and heart transplant
- Re-existing hyperlipidemia, DM, HTN, family Hx, renal dysfunction, diet, smoking, obesity, age > 50, male, medications (β-blockers, sirolimus, steroids, cyclosporine more than Tacrolimus), hypothyroidism are risk factors.
Post-transplant Hyperlipidemia

• Statins + immunosuppressive drugs ⇒ ↓ acute rejection episodes in heart transplantation
• The lipid-lowering agent of choice for transplant pts are statins
  • Atorvastatin (max. 40 mg)
• Ezetimibe
Post-transplant DM

- Affects morbidity and mortality
- Prevalence 3-40%
- Most cases occurring within the 1st year

Risk factors:
- pre-transplantation DM,
- advanced age,
- family Hx,
- CMV infection,
- certain HLA,
- race,
- ↑Wt
Post-transplant DM

- Drugs: CNI\(s\) especially tacrolimus, Steroids
- CNI\(s\) have direct toxic effects on pancreatic \(\beta\) cells
  \(\Rightarrow\) \(\downarrow\) insulin synthesis
- Dose dependent
- Reversible
Post-transplant osteoporosis

**Risk factors:**

- Menopausal status
- Family Hx
- Smoking
- Alcohol
- Lack of physical activity
- Poor nutrition
- Medications (steroids, phenytoin, thyroxin, heparin, warfarin, loop diuretics)
- Preliminary disease (renal osteodystrophy)
Post-transplant osteoporosis

- Most common in 3-6 mo after transplant (when the steroid dose is high)
  
  - Ca 1500 mg/d & Vit. D
  
  - Biphosphonate or calcitonin if ↓BMD
Secondary Malignancies

- PTLD as a result of intensity of immunosuppression, EBV and age (more in children)
- The majority is non-Hodgkin’s lymphoma primarily of B-cell origin
- Skin cancer
- Lip cancer
- Attributed to sun exposure after skin sensitization to sunlight by AZA
Usual Infection Prophylaxis

• Infection risk is highest during the first 6 mo after transplantation due to highest dose of immunosuppressive drugs

• Another high risk time is during & after Tx of acute rejection
Usual Infection Prophylaxis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Time of onset after transplant</th>
</tr>
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<tr>
<td>CMV</td>
<td>1-6 mo</td>
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<tr>
<td>HSV</td>
<td>2 wk-2 mo</td>
</tr>
<tr>
<td>EBV</td>
<td>2-6 mo</td>
</tr>
<tr>
<td>VZV</td>
<td>2-6 mo</td>
</tr>
<tr>
<td>Fungal</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>PCP</td>
<td>1-6 mo</td>
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Ganciclovir
Usual Infection Prophylaxis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Time of onset after transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listeria</td>
<td>1 mo–indefinitely</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>1-4 mo</td>
</tr>
<tr>
<td>Nocardia</td>
<td>1-4 mo</td>
</tr>
<tr>
<td>Toxo</td>
<td>1-4 mo</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>4 mo–indefinitely</td>
</tr>
</tbody>
</table>
Usual Infection Prophylaxis

- Nystatin 500’000 U, TID-QID or Fluconazole 100 mg/d
- Acyclovir
- Ganciclovir, valganciclovir, CMV Ig
- TMP-SMX for PCP
- These regimens generally for 3-6 mo or in some cases 1 year or even life-long
Usual Infection Prophylaxis

**Immunization:**
- Yearly flu vaccine
- Pneumococcal vaccine
- Avoid live vaccines (Hepatitis A, …)

Sometimes it is necessary to ↓ or DC immunosuppression until end of infection Tx
Usual Infection Prophylaxis

- **CMV** (most common opportunistic infection in solid organ transplant pts) ⇒
  - ↑risk of bacterial & fungal infection
  - Chronic injury to transplanted organ