Transplantation

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Objectives

1. Recognize corresponding brand/generic names for medications used in solid organ transplant.
2. Recall risk factors for transplant rejection.
3. Discuss available immunosuppressive therapies including:
   - Mechanism of action
   - Notable adverse effects
   - Potential drug-drug interactions
   - Recommendations for levels
   - Clinical pearls
4. Describe how to treat potential cardiovascular complications post-transplant.
5. Recognize medications used to prevent infectious complications post-transplant.
6. Synthesize an appropriate patient care plan when given a patient case.

Most Commonly Transplanted Organs

- Heart
- Kidney
- Liver
- Lung
- Pancreas
- Intestine

Main Reasons for Transplantation

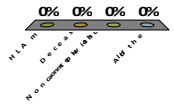
- Heart
  - NYHA Class III and IV typically developed from idiopathic cardiomyopathy and ischemic heart disease
- Kidney
  - Diabetes, HTN and glomerulonephritis leading to ESRD
- Liver
  - Noncholestatic cirrhosis (hepatitis C, alcoholic cirrhosis, hepatitis B, nonalcoholic steatohepatitis and autoimmune hepatitis)

Background

- What is the main risk a patient encounters post transplant?
  - Transplant rejection
- What two ways do we use to reduce transplant rejection?
  - Serotyping to determine most appropriate donor-recipient match
  - Immunosuppressants

Which one of the following are risk factors for transplant rejection?

A. HLA mismatch
B. Deceased donor
C. Noncompliance with immunosuppressive regimen
D. All of the above



Risk Factors for Transplant Rejection

- HLA mismatch (kidney)
- Previous sensitization
  - History of pregnancy
  - Previous transplant
  - Previous rejection
  - PRA > 20%
- African American ethnicity
- Pediatric patients
- Deceased donor
- Prolonged preservation time of organ
- Noncompliance with medication regimens
- Donor age (> 60 yo)
- ABO mismatch

Mechanism of Graft Rejection

- Key event: T-cell activation
  - T-cells infiltrate the graft producing inflammatory/cytotoxic effects
  - Macrophages produce tissue damage
- Four types
  - Hyperacute Rejection
  - Acute Cellular Rejection
  - Humoral Rejection (antibody mediated)
  - Chronic Rejection

Presentation of Rejection

- General Symptoms
  - Chills
  - Body aches
  - Nausea
  - Cough
  - SOB
- Organ-specific Symptoms
  - HF symptoms
  - Atrial arrhythmias
  - ↑ SCr ≥ 30% baseline, ↓ UOP
  - Fluid retention, edema
  - Hypertension
  - Change in bile
  - Serum bilirubin > 50% baseline
  - LFTs 3x ULN

Immunosuppressants

- Calcineurin Inhibitors (CIs)
  - Cyclosporine (Sandimmune, Neoral)
  - Tacrolimus (Prograf, Astagraf XL)
- Steroids
  - Methylprednisolone (Solu-Medrol)
  - Prednisone (Deltasone)
- Antimetabolite agents
  - Mycophenolate mofetil (Cellcept)
  - Mycophenolate sodium (Myfortic)
  - Azathioprine (Imuran)

Immunosuppressants (cont.)

- mTOR inhibitors (mammalian target of rapamycin)
  - Sirolimus (Rapamune)
  - Everolimus (Zortess)
- Monoclonal antibody
  - Muromonab-CD3 (OKT3) – withdrawn from market
  - Basiliximab (Simulect)
- Polyclonal antibody
  - Antithymocyte globulin (Atgam, Thymoglobulin)
- IL-2 receptor antagonist
  - Belatacept (Nulojix)

Induction Therapy

- Why do we use induction therapy?
  - Prevent acute rejection immediately post transplant
- What are the strategies?
  - Provide high level immunosuppression based on patient-specific RF
  - Antibody therapy to delay the use of CIs post-transplant
- Most common agent – basiliximab
- If patient is at higher risk of acute rejection
  - basiliximab + antithymocyte globulin
- May not be necessary if patient is receiving isograft

Maintenance Therapy

- **GOAL**: prevent acute and chronic rejection while reducing toxicities of the immunosuppressive agents
- CIs are typically the base of immunosuppressive treatment
- Regimen based on factors such as:
  - Transplant organ and type
  - HLA mismatch
  - Time after transplantation
  - Post-transplant complications
  - Previous immunosuppressive adverse reactions
  - Compliance
  - Financial situation

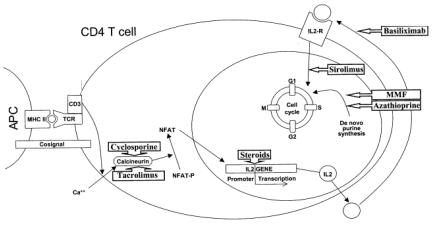
Maintenance Regimens

- Double Therapy:
  - CI + steroids
  - CI + antimetabolite
  - CI + mTOR inhibitor
  - mTOR inhibitor + steroids
  - mTOR inhibitor + antimetabolite
  - Antimetabolite + steroids

Maintenance Regimens (cont.)

- Triple Therapy:
  - CI + antimetabolite + steroids
  - mTOR inhibitor + CI + steroids
  - mTOR inhibitor + antimetabolite + steroids
  - Costimulation blocker + antimetabolite + steroids

Targets of Immunosuppressive Therapy



Cyclosporine (Sandimmune, Neoral)

- MOA: stops T-cell proliferation by inhibiting calcineurin and blocking IL-2 production
- Drug-Drug interactions:
  - Substrate and inhibitor of CYP3A4 and P-gp
  - Grapefruit juice
- Clinical Pearls:
  - Requires bile for emulsification/absorption (Sandimmune > Neoral)
  - Neoral formulation forms microemulsion with aqueous fluids in the GI tract = less dependence on bile for absorption
  - Therefore, Sandimmune and Neoral are **NOT** interchangeable
  - Recommended to use 3:1 ratio when Δ from oral to IV

Tacrolimus (Prograf, Astagraf XL)

- Tacrolimus in >80% of immunosuppressive regimens (excluding heart transplant)
- MOA and Drug-Drug interactions:
  - Same as cyclosporine
  - Inhibitor of CYP3A4 (< cyclosporine)
- PK: 99% protein bound – mainly albumin
- Clinical pearls:
  - Astagraf XL (once daily formulation) was approved in July 2013 for prophylaxis of organ rejection in kidney transplant patients
  - Take on an empty stomach

CI Adverse Effects

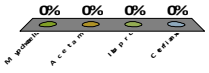
- Cyclosporine:
  - **Nephrotoxicity**
  - **Gingival Hyperplasia**
  - Hirsutism
  - Tremor
  - Hyperglycemia
  - Hyperlipidemia
  - Hypertension
  - QT prolongation
- Tacrolimus:
  - **Nephrotoxicity**
  - Diarrhea, nausea
  - Hepatotoxicity
  - Tremor, headache
  - Hyperglycemia
  - Hypertension
  - ↑ K, ↓ Mg
  - QT prolongation

CI Nephrotoxicity

- Two types: acute and chronic
  - Acute – reversible, dose dependent, seen early post-transplant
- Mechanism
  - Renal vasoconstriction (afferent arteriole) = increased vascular resistance = decreased renal blood flow by up to 40% = decreased GFR up to 30%
- Why does this matter?
  - Must be careful to watch out for concurrent nephrotoxic agents

Used concurrently with tacrolimus, which medication can increase the risk of nephrotoxicity?

A. Mycophenolate
B. Acetaminophen
C. Ibuprofen
D. Ceftriaxone



Corticosteroids (Solu-Medrol, Deltasone)

- Cornerstone of therapy
  - Part of regimen in 40% of liver transplants, 70% of kidney transplants
  - Methylprednisolone (Solu-Medrol), Prednisone (Deltasone)
- MOA: block cytokine activation which inhibits proliferation of IL-2
- Drug-Drug Interactions: metabolized via CYP3A
- Clinical Pearls:
  - Give prednisone between 7-8 am to mimic normal cortisol release
  - May eventually be tapered off, but more commonly, the patient will stay on corticosteroids for the life of the graft

Corticosteroid Adverse Effects

- Short-term adverse effects:
  - Increased appetite (↑ wt)
  - Insomnia
  - Indigestion
  - Mood changes
  - Leukocytosis
  - Hyperglycemia
  - Fluid retention
- Long-term adverse effects:
  - Hirsutism
  - Bruising
  - Hypertension
  - Bone growth suppression
  - Ulcerative esophagitis (GI bleeding)
  - Hyperlipidemia
  - Impaired wound healing
  - Adrenal suppression/Cushing's syndrome

Mycophenolic acid (MPA)

- Mycophenolate mofetil (Cellcept), Mycophenolate sodium (Myfortic)
- MOA: reduces lymphocyte production by inhibiting de novo purine synthesis
- PK: unstable in acidic environment
  - Cellcept is a prodrug & Myfortic is enteric coated
- Clinical pearls:
  - Cellcept and Myfortic **NOT** used interchangeably – absorption differences
  - Azathioprine >> mycophenolic acid for hematologic adverse effects
  - Myfortic approved for kidney transplants only
  - Key element in CI-sparing protocols
  - Take on empty stomach

Mycophenolic acid (cont.)

- Common/serious adverse effects:
  - N/V, diarrhea, abdominal pain (less with Myfortic)
  - Hematologic (leukopenia, anemia) – more common with high doses
  - Progressive multifocal leukoencephalopathy (PML)
- Drug-Drug interactions:
  - Use with antacids/cholyestyramine not recommended (↓ AUC MPA)
  - Acyclovir competes for renal tubular secretion – ↓ AUC of both
  - Concurrent use with cyclosporine can cause ↓ trough [ ] of MPA
    - ***NOT seen with tacrolimus, sirolimus
  - Can ↓ levels of hormonal contraception

Azathioprine (Imuran)

- Prodrug converted to 6-mercaptopurine (6-MP)
- MOA: incorporated into purine synthesis and halts **BOTH** the salvage and de novo pathways of DNA, RNA and protein synthesis
- Adverse effects:
  - **Hematologic** (leukopenia, anemia, thrombocytopenia)
  - Alopecia
  - Hepatotoxicity
  - Pancreatitis
- Drug-Drug interactions:
  - Allopurinol can ↑ azathioprine and 6-MP [ ] 4x

Sirolimus (Rapamune)

- MOA: binds to mTOR, inhibits cell response to IL-2 which inhibits T-cell proliferation
- Indication: prophylactic in kidney transplant (off-label: heart transplant)
- Drug-Drug, Drug-Food interactions:
  - Substrate of CYP3A4 and P-gp and inhibitor of P-gp
  - Concomitant use with Neoral ↑ AUC/trough sirolimus (separate by 4 hrs)
    - NOT seen with Sandimmune or tacrolimus
  - High fat meal = delayed absorption, ↓ C_{max}, ↑ AUC
- Clinical Pearls:
  - Can be combined with mycophenolate to prevent use of CIs
  - Take at same time each day, with or without food

Everolimus (Zortess)

- MOA: same as sirolimus
- Indicated for prophylactic use in kidney and liver transplants
- Drug-Drug, Drug-Food interactions:
  - Substrate and inhibitor of CYP3A4 and P-gp
  - High fat meal = ↓ C_{max} and AUC
- Clinical pearls:
  - Must reduce the dose of cyclosporine when used concurrently with everolimus
  - Same administration recommendations as sirolimus

mTOR Inhibitor Adverse Effects

- Sirolimus
  - **Hyperlipidemia**
  - Delayed wound healing
  - Pneumonitis/bronchitis
  - Cough
  - Hyperglycemia
  - Thrombocytopenia
  - Leukopenia
- Everolimus
  - **Hyperlipidemia**
  - Delayed wound healing
  - Pneumonitis
  - Hyperglycemia
  - Hypertension
  - Peripheral edema
  - Constipation

Basiliximab (Simulect)

- MOA: chimeric monoclonal antibody that inhibits the IL-2 receptor on the surface of activated T-cells (immediate)
- **If used during induction therapy, CI therapy can be delayed or started at a lower dose**
- Drug-Drug Interactions:
  - Can see ↑ cyclosporine and tacrolimus levels

Basiliximab Adverse Effects

- Hypertension
- Fever, Weakness
- Abdominal issues
- Peripheral edema
- Dyspnea/upper respiratory irritation, infection
- Tremor
- Painful urination

Antithymocyte globulin (Atgam, Thymoglobulin)

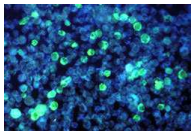
- MOA:
  - Binds to lymphocyte receptors (eg. CD3) causing complement-mediated lysis and lymphocyte depletion ("depleting antibody")
- Both formulations commonly used in induction therapy and acute allograft rejection for kidney transplants
- Clinical Pearls:
  - Each preparation of polyclonal antibodies contains a variable amount of antibodies = variable efficacy and risk of side effects
  - Premedication may be required due to anaphylactic risk

Antithymocyte Adverse Effects

- Dose-limiting myelosuppression
- Anaphylaxis
- Hypo/hypertension
- Tachycardia
- Dyspnea
- Urticaria
- Rash
- Serum sickness (Atgam > Thymoglobulin)
- Nephrotoxicity – rare and usually in presence of serum sickness

Belatacept (Nulojix)

- Indicated for rejection prophylaxis post-kidney transplant
- MOA - referred to as a T-cell co-stimulation blocker
  - Binds CD80 and 86 on antigen presenting cells blocking their interaction with CD28 on T-cells and preventing activation
- Clinical Pearls:
  - **MUST** use in Epstein-Barr virus seropositive patients **ONLY**
    - Patients who are EBV seronegative are at ↑ risk for post-transplant lymphoproliferative disease (PTLD)
  - Should not be used in liver transplant patients due to ↑ risk of rejection/death



Belatacept Adverse Effects

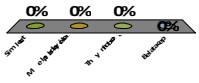
- Anemia, leukopenia
- Nausea, diarrhea, constipation
- Peripheral edema
- Hypertension
- Cough
- Photosensitivity
- Headache
- Insomnia
- UTIs
- Pyrexia
- Hypo/hyperkalemia

Which immunosuppressants need levels performed?

- **Cyclosporine, Tacrolimus**
  - Trough levels are dependent on type of transplant, time after transplant & concomitant immunosuppressive agents
  - Should be done daily to 3x week initially → monthly once stable
- Sirolimus
  - Recommendation to check level if physician is changing the cyclosporine dose or removing it from regimen

Which agent can be used with the hope of delaying nephrotoxicity in renal transplant patients?

A. Simulect
B. Methylprednisolone
C. Thymoglobulin
D. Belatacept



Post-transplant Complications

- Rejection
- Non-infectious complications
- Infectious complications

Treatment of Acute Rejection

- Primary Goal: minimize reaction and avert further injury to graft
- 4 options for treatment:
  1. Increase doses of current immunosuppressive agents
  2. Pulse dose corticosteroids and then taper
  3. Add additional immunosuppressive agent to regimen
  4. Provide short term treatment with polyclonal or monoclonal antibody
- Most patients will receive pulse of high dose corticosteroids
  - 500-1000 mg IV Solu-Medrol for 1-3 doses

Non-infectious Complications

- Causes of mortality in patients with a functioning graft ≥ 5 yrs
  - Cardiovascular disease
  - Malignancy
  - Recurrent disease
  - Drug toxicities (nephrotoxicity)
  - Chronic rejection

Cardiovascular Disease

- Preexisting CV disease not altered by transplantation
- HTN, HLD, diabetes are common complications
  - independent risk factors for the development of CV disease
- Adverse effects of immunosuppressive agents
  - Hypertension – corticosteroids, CIs
  - Hyperlipidemia – corticosteroids, CIs, mTOR inhibitors
  - Hyperglycemia – corticosteroids, CIs

Hypertension

- First line therapy:
  - Calcium channel blockers
    - Increased risk gingival hyperplasia with cyclosporine
  - ACEIs/ARBs – must monitor RF and potassium
    - If SCr ↑ > 30% in the two weeks after initiation post-transplant = discontinue
- Second line agents:
  - Beta blockers – can cause further metabolic disturbances
  - Diuretics
  - Centrally acting agents

Hyperlipidemia

- First line therapy:
  - Dietary modification
  - Statins – also have immunomodulatory effects
- Drug-Drug interactions
  - Statins – CIs = ↑ risk of rhabdomyolysis
    - Pravastatin can be used due to lack of CYP3A4 metabolism
  - Bile acid-binding resins
    - Separate dose from cyclosporine by ≥ 2 hrs
    - Good recommendation to separate them from ALL immunosuppressants by ≥ 2 hrs to avoid adsorption in GI tract

New-onset diabetes after transplantation (NODAT)

- Occurs in 4-20% patients
  - Corticosteroids – induce insulin resistance, impair peripheral glucose uptake
  - CIs – inhibit insulin production (tacrolimus > cyclosporine)
- Clinical Pearls:
  - Choose hepatically eliminated > renally eliminated diabetic agents
  - Caution with metformin – risk of lactic acidosis with renal impairment
  - Monitor BG often immediately post-transplant
    - Early identification of patients with NODAT
    - Improve glucose control
  - Counsel on signs/symptoms of hypo/hyperglycemia

Infectious Complications

- Important cause of morbidity/mortality
- Linked to type of organ transplant/immunosuppression
- Common prophylactic post-transplant medications:
  - **Valganciclovir** (**Valcyte**) – prevention of **Cytomegalovirus** (CMV)
  - **Bactrim** – prevention of ***Pneumocystis Jiroveci*** pneumonia (PCP)
  - Antifungal – prevention of *Candida, Aspergillus* etc.
    - Actual choice depends on type of transplant, location

Case Presentation

- RD is a 71 yo AA male s/p cadaveric kidney transplant 10 yrs ago
- **CC**: left hand is turning black
- **HPI**: RD was a HD patient while waiting for a kidney transplant. He has retained a patent AV fistula in case the transplant failed and he needed to begin HD again. He started having pain below the fistula on his arm 3 days ago. At the same time the pain developed, his skin started turning black.
- **PMH**: CKD s/p cadaveric kidney transplant 10 years ago (baseline SCr ~1.1), hypertension, diabetes, hyperlipidemia, anxiety
- **Current Medications**:
  - Prograf, Myfortic, prednisone, Pravachol, lisiniopril, metformin, Lantus, Ativan prn, Vitamin D, furosemide, KlorCon

Case Presentation (cont.)

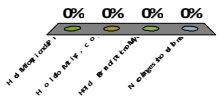
- Labs:

143	110	20	147
5.2	22	1.68	

- A/P:
  - Suspect a blockage below the AV fistula
  - Decide to give the patient the option of undergoing a procedure utilizing IV contrast to determine the presence of a clot
- What is the risk the patient faces with this decision?

When the physician asks what you think about RD's immunosuppressive regimen, what recommendation do you make?

A. Hold Myfortic and Prograf
B. Hold Myfortic, continue Prograf
C. Hold Prograf, continue Myfortic
D. No changes should be made



What other recommendations would you like to make to the physician?

- Hold metformin
  - SCr > 1.5 (men) – increased risk of lactic acidosis
- Hold lisinopril
  - Currently in AKI
- Hold KlorCon
  - Potassium is 5.2, in AKI with risk of further increasing SCr due to IV contrast
- Watch for hyperglycemia
  - BS already elevated and holding metformin

Questions??

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