Introduction to Kidney Transplantation: Hospitalist Lecture

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Medical Director
UCI Kidney Transplant Program
November 5th, 2018
Learning Objectives

• Introduction to the UCI Kidney Transplant Program
• Background & Importance of Transplantation
• Common Post Transplantation Issues
• Immunosuppression
• Vaccinations
• Key drug-drug interactions
• Summary
Welcome to the UCI Kidney Pancreas Transplant Program
UCI Irvine Kidney Transplant
Physician Leadership

Donald Dafoe, MD
Transplant Surgeon
Surgical Director

Hirohito Ichii, MD
Transplant Surgeon

Uttam Reddy, MD
Transplant Nephrologist
Medical Director
Latest Hire November 2017

Ekamol Tantisattamo, MD
0.5 General Nephrologist
0.5 Transplant Nephrologist
Program Overview

- UCI has been involved with kidney transplantation for the past 40 years.
- In Fiscal year, we did a UCI all time high **110 total organ transplants**, including **7 Kidney Pancreas transplants**!
- This is double our growth from last year, and triple our growth from 2 years ago.
- **Fasted Growing Transplant Program in California, for programs that have done >50 transplants.**
- Current # of Wait Listed Patients: Close to 700 patients
- SRTR Outcomes Assessment score of 4/5 for the past 2 years (better than expected, same score as UCLA for the past 2 years)
General Vision

• To continue to grow and expand the UCI Kidney Transplant program to be a valuable resource for ESRD patients in Orange County and Southern California.

• Provide quality, high level care throughout the growth period

• Have a larger role in the landscape of Transplant services across the region, which we see is happening over the past couple years.
UC Irvine Dialysis Center:

*Has grown to become the 3 largest dialysis centers in OC since 2014!*

The OC has 41 dialysis centers with n=4,367 dialysis patients
Some of the Many Changes at UCI

- Dr. Reddy - New Medical Director July 2015
- Dr. Donald Dafoe – Chief Surgical Director started July 2017
- Anne Marie Lutrick – Administrative Director started May 22nd
- Addition of more staff – social worker, coordinators, NPs, financial team, etc.
- Revamped Pre Transplant Evaluation Process
- Waitlist Management Tiered System
- Post Transplant Immunosuppression Protocols
- Post Transplant Infectious Screening
- Close Post transplant follow up
- Decreased Re-admission Rates
- Hepatitis C Kidney Transplants (featured in AJT in October 2018)
- Increased Kidney Pancreas Transplants
The transplantation of HCV-positive organs into HCV-positive patients appears to be safe, but there are theoretical risks. For example, the organ may be infected with a different strain of virus from the one that infects the recipient, in which case the transplant could theoretically complicate treatment of the recipient’s infection. In most cases, transplant providers do not know the donor’s HCV strain and are thus unable to protect against this potential consequence. Although such a risk may seem trivial to a patient facing a decade of dialysis, patients who anticipate only a year on the waitlist before they can receive an HCV-negative organ may decide to forgo the incremental risk.
UCI Experience

• In the past 2.5 years at UCI, we have done 10 Hep C transplants (close to 5-10% of all our transplants during that time).
• All 10 have been treated post transplant with negative viral loads
• 4 of the patients were transplanted within 1 week of being listed for Hepatitis C Kidneys
Multi-Disciplinary Approach

- Transplant Surgeons
- Transplant Nephrologists
- Social Workers
- Transplant pharmacist
- Dietician
- Nursing Coordinators
  - Pre Transplant, Wait-List, Post-Transplant
- **Internal Medicine (PCP, inpatient hospitalizations)**
- General Nephrologists/Dialysis Unit Team
- Cardiology (pre and post transplant)
- Endocrinology (post transplant diabetes)
- Infectious disease (pre and post transplant)
- Hematology/Oncology (pre and post)
- Interventional Radiology
- Pathology
- Administrative support
I. Background & Importance of Transplantation
Kidney Transplantation: A relatively new field

• The first kidney transplant surgery was in December 1954 (~64 years ago) at what is now Brigham and Women’s Hospital in Boston.

• The recipient, who received the kidney from his identical twin, lived for 8 more years.

• The lead surgeon, Dr. John Murray was eventually awarded the Nobel Prize for his work in organ transplantation.
5 year Dialysis Survival: 35%

USRDS Data
Treatment Modality in ESRD Patients Alive Beyond 10 Years

- Transplantation: 69%
- Hemodialysis: 28%
- Peritoneal dialysis: 3%

Expansive Waitlist Growth

**Kidney transplants**
The number of patients awaiting kidney transplants has far outpaced available organs from donors.

- **Awaiting transplant**
- **Living donor**
- **Deceased donor**

100 thousand

![Graph showing the number of kidney transplants over time, with a significant increase in the number of patients awaiting transplantation compared to living and deceased donor contributions.](chart.png)

*Source: Organ Procurement and Transplantation Network*
WAITING LIST BY ORGAN

Waiting List Candidates by Organ Type - All Patient States

Based on OPTN data as of July 6, 2017

<table>
<thead>
<tr>
<th>Organ</th>
<th>Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>97,249</td>
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<tr>
<td>Liver</td>
<td>14,351</td>
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<tr>
<td>Pancreas</td>
<td>905</td>
</tr>
<tr>
<td>Kidney / Pancreas</td>
<td>1,704</td>
</tr>
<tr>
<td>Heart</td>
<td>3,947</td>
</tr>
<tr>
<td>Lung</td>
<td>1,371</td>
</tr>
<tr>
<td>Heart / Lung</td>
<td>36</td>
</tr>
<tr>
<td>Intestine</td>
<td>263</td>
</tr>
<tr>
<td>Total</td>
<td>117,218</td>
</tr>
</tbody>
</table>

- Kidney: 81.2%
- Liver: 12%
- Pancreas: 0.03%
- Kidney / Pancreas: 0.02%
- Heart: 0.01%
- Lung: 0.02%
- Heart / Lung: 0.003%
- Intestine: 0.02%
Waitlist Statistics

• Currently 117,000 people waiting for lifesaving organ transplants in the US
  – Close to 100,000 are on the KIDNEY transplant waitlist

• In 2016, 19,062 kidney transplants took place in the United States (the most ever).

• The Greater Los Angeles area is represented by the One Legacy Organ Procurement Organization.
ONE LEGACY Kidney Wait Times by Blood Group

- O Blood Group: 10 Years
- A Blood Group: 7-8 years
- B Blood Group: 8-10 years
- AB Blood Group: 5-6 years

*Wait time starts from first day on dialysis or date of listing (whichever one comes first)*
Yearly Total Kidney Transplants

Kidney Transplant from Living Donors, by Donor Relation

Graph showing the number of transplants over years for different donor relations:
- Related
- Distantly related
- Spouse/partner
- Paired donation
- Other unrelated
- Unrelated directed

Years: 1998 to 2012

Transplants range from 0 to 4,000
Kidney Transplant Paired Donation

Paired Donation

Pair 1
- Donor 1 → Recipient 1 (compatible)
- Not compatible

Pair 2
- Donor 2 → Recipient 2 (not compatible)
Kidney Transplant “Chain”
New Creative Ways in Dealing with Organ Crisis: Voucher Program

• Voucher program backstopped by the Kidney Registry (NKR)

• 44 Transplant Centers have joined Voucher/Advanced Donation Program

• 80+ Transplants have been facilitated from voucher donors triggering chains
  – Cornell, UCLA are the biggest ones
  – UCSF, Scripts have been involved.
Voucher Program Stats (June 2018)

- 2 vouchers have been redeemed
- The redeemed voucher holders were A and O blood types
- The kidneys were allocated from the end of other chains.
- Voucher redemption to transplantation was 63 and 65 days.
- Many vouchers will never be redeemed.
Absolute/Relative Contraindications to Kidney Transplantation

- Active infection
- Recent Malignancy
- Uncontrolled psychiatric disorders
- Lack of social support
- Substance abuse
- Severe or Irreversible heart-lung-liver disease
  - Can be considered for dual organ transplant
- AGE ?????
  - Some centers have age <70.
  - UCI will evaluate them on a case by case basis.
Kidney Transplant Costs Less

Annual ESRD Treatment Costs per Patient for HD, PD, Transplantation (Tx), and all ESRD

- **Cost**
  - $100,000
  - $90,000
  - $80,000
  - $70,000
  - $60,000
  - $50,000
  - $40,000
  - $30,000
  - $20,000
  - $10,000

- **Year**
  - 2006
  - 2007
  - 2008
  - 2009

- **Legend**
  - HD
  - PD
  - Tx
  - All ESRD
Quality of Life Benefits

- Relatively unrestricted diet
- Freedom to Travel
- Ability to become pregnant, have children
- Lifestyle free of dialysis constraints.
- Engage in more physical activity
Importance - Summary

• Compared to remaining on dialysis patient’s undergoing kidney transplantation
  – Live longer
  – Have a better quality of life
  – Save on overall medical costs

• Kidney Transplantation is the optimal therapy for ESRD patients who can undergo transplantation
BASICS OF KIDNEY TRANSPLANT MANAGEMENT
Types of Kidney Transplants

• Living Donor
  – Related
  – Unrelated/Altruistic
  – Pre-emptive
    • Before starting dialysis

• Deceased Donor
  – Directed
  – KDPI < 85%
  – KDPI > 85%
  – Pediatric
  – Dual Kidney
  – Public Health Service (PHS) High Risk
  – Death after Cardiac Death (DCD)
  – Hepatitis C
Typical Follow up

- Assuming no major post transplant issues, patients are followed up:
  - Twice a week for the first month
  - Once a week for the second month
  - Every 2 weeks for the third month
  - Every 1-3 months for the first year.
  - After 1 year, some centers follow annually.
  - At UCI, we follow every 3 months for the first 3 years.
  - Primary nephrologist/PCP usually get involved in patients care after 3-6 months post transplantation.
Importance of Close Follow Up

• Dosing of immunosuppressive medications
  – Tacrolimus/CsA, steroid tapering
• Assessing allograft function
  – Creatinine
  – Urine Protein
• Screening/Monitoring for infections
  – CMV, BK virus
• Bone Mineral Disease
  – PTH, Vitamin D, Ca, P
• Risk for malignancy
  – Skin cancer
  – PTLD
  – Age appropriate cancer screening
COMMON POST TRANSPLANT ISSUES
Typical Post Transplant Complications

- Allograft dysfunction
  - Elevated Creatinine or Proteinuria
- Side effects of immunosuppression
- Co-morbidities
  - DM, HTN, Recurrent disease
- Infectious disease
- Anemia
- Cardiovascular Disease
- Malignancy
Elevated Baseline Creatinine

- Following transplantation, baseline creatinine tends to be higher than 1.1, which is equivalent to a GFR of less than 60 ml/min per 1.73m²
  - Single Kidney
  - Ischemic injury (deceased donor)
  - Quality of the Kidney (Elevated KDPI)
  - Use of Calcineurin inhibitors – Vasoconstriction, ATN
  - Size mismatch
Causes of Allograft Dysfunction

- Pre Renal
  - Over-diuresis or under hydration
  - Diarrhea/GI issues
- Post Renal Obstruction
- CNI Toxicity
- Allograft rejection
- Recurrent Glomerulonephritis
- De Novo Renal Diseases (ATN, toxins)
- Drug induced AIN
- Renal Artery Stenosis
- Infection
  - Pyelonephritis
  - BK nephropathy
Acute Allograft Rejection

- Two Categories of Acute Rejection
  - Cellular (ACR) and Antibody mediated (AMR)

- Acute Cellular Rejection
  - Interstitial infiltration with mononuclear cells and occasionally eosinophils, and disruption of the tubular basement membranes by the infiltrating cells (lymphocytes, plasma cells, etc)
  - Tubulitis and intimal arteritis are the primary lesions.

- Antibody Mediated Rejection
  - Capillary endothelial swelling, peritubular capillaritis, arteriolar fibrinoid necrosis, fibrin thrombi in glomerular capillaries, and frank cortical necrosis in severe cases.
  - Donor Specific Ab
  - C4d staining on biopsy – highly suggestive of AMR
Pathology Slides

Acute Cellular rejection

Ab-mediated rejection
Treatment of Acute Rejection

• Acute Cellular Rejection
  – For simple ACR, treatment is pulse dose steroids x 3 days, followed by oral steroid taper
  – If rejection is more severe (significant tubulitis, vascular involvement), treat with Thymoglobulin x 5-7 days.
  – Goal Tacrolimus increases to 8-10 ng/ml during rejection.

• Antibody Mediated Rejection
  – Plasmapheresis and IVIG
  – If severe, can consider Rituximab
  – More recent studies looking into Eculizumab
  – Monitor Donor Specific Antibodies
Proteinuria

- **Recurrent Disease**
  - FSGS – 30%
  - IgA Nephropathy – 10-30%
  - Membranous 10-30%
  - Diabetes

- **De Novo Disease**
  - Transplant Glomerulopathy
  - Secondary FSGS
  - Diabetes
Focal Segmental Glomerulosclerosis

Resolution of Recurrent Focal Segmental Glomerulosclerosis after Retransplantation

Gallon L, et al. NEJM, 2012; 366, 1648
FSGS: Risk Factors for Recurrence

- Childhood onset of initial FSGS disease.
- Rapid progression of initial disease.
- White race.
- Hx of recurrence in a prior allograft.

- Less frequent in African American populations.
- White recipients of African American kidneys at a higher risk.
- Histological subtype does not predict recurrence.
- Family history of FSGS - low risk of recurrence.
Renal Biopsy Indications

• Concern for rejection
• Unexplained rise in creatinine
• Concern for BK nephropathy
• Evaluate for recurrent disease
• Proteinuria exceeding 1 gram/day
• Protocol Biopsy

• Risk of biopsy
  – Bleeding, Damage to other organs, infection, loss of allograft.
  – Complication rate on the order of 0.4-1%
  – Graft loss occurs in 1/2500 biopsies.

Furness PN, et al. Transplantation, 2002
Infectious Complications

• Major cause of graft loss and death
  – Common Infections
  – Opportunistic Infections

• Higher risk in months 1-3 given that’s when immunosuppression is at its maximum.

• Can occur anytime, as long as immunosuppressed.
Urinary Tract Infection

• High incidence of complicated UTIs

• Recurrent UTIs
  – Imaging of Transplanted and Native kidneys
  – Cystoscopy, Referral to Urology/Uro-Gyn
  – Vaginal estrogen creams in post-men female
  – Preventive behavioral changes
  – Vitamin C, Hiprex

• ESBL E.Coli Infection
  – Treatment with IV Carbapenem, Cefepine, occasionally Zosyn
  – Oral treatment with Fosfomycin
  – Please do NOT treat with Macrobid (despite what sensitivities show)
Common Opportunistic Infections

- **Cytomegalovirus (CMV)**
  - Hepatitis, Retinitis, PNA, encephalitis, GI Ulcerations
- **Polyomavirus (BK and JC virus)**
  - Viruria, Viremia
  - BK Nephropathy
- Pneumocystis jirovecci pneumonia (PCP)
- Coccidiomycosis in patient who have prior history
- Tuberculosis. Try to treat prior to transplant
- Varicella – Shingles is common post transplant complication
- All transplant patients receive prophylaxis for CMV and PCP infections.
BK Viremia & Nephropathy

- Polyomaviruses – ubiquitous, small, non-enveloped double stranded DNA virus. Highly seroprevalent in humans but only cause clinical disease in immunocompromised patients
  - 60-80% seroprevalence
- BK screening important in the first year
- BK viremia can lead to BK nephropathy in up to 10% of patients.
- Treatment revolves around lowering immunosuppression.
  - Leflunomide
  - Ciprofloxacin
CMV Infection

- CMV screening is also important in the first year
- Prophylaxis is given for 3-6 months
  - Valcyte 450mg-900mg daily (renally dosed)
- Highest risk CMV scenario [D(+), R(-)]
  - Will need 6 months of prophylaxis
  - Induction agent matters (Thymo higher risk)
- Treatment of CMV viremia – Valcyte 900mg BID x 21 days, followed by 900mg daily x 1 month
- If evidence of end-organ disease, treat with IV Ganciclovir at a dose of 5mg/kg for up to 2-4 weeks.
Whatchu Know about NODAT?

• New Onset Diabetes after Transplant (NODAT)
• Insulin metabolism and excretion
  – Hidden Diabetes
• Transplanted kidney – gluconeogenic
• Immunosuppression increase blood sugars
  – Tacrolimus
  – Steroids
• Pre-existing risk factors predispose to DM
NODAT

• Develops within the first few months
• Continued risk for life of patient & allograft
• Monitor fasting blood sugars and check HgBA1C accordingly
• Some Centers check HgBA1c at 3, 6, and 12 months, and annually thereafter.

• Treat with diet modifications, exercise, weight loss, pharmacological options
Malignancy

• Cancer after transplantation is 3x more likely than general population.

• These cancers have 5 fold or > increase in transplant patients
  – Kaposi Sarcoma
  – Skin Cancer
  – Non-Hodgkin Lymphoma
  – Liver
  – Anus/Lip/Vulva

• Malignancy represents the 3rd most common cause of death in renal transplant recipients.
Cause-Specific Rates of Death with Function 2005-2010

- Unknown
- Cardiovascular
- Malignancy
- Not Reported
- Other
- Infection
- Miscellaneous
- Cerebrovascular
- Hemorrhage
- Trauma
- Graft Failure

Rate per 100 person-years

Year Post-Transplant
Skin Cancer

• Highest risk is for skin cancer
  – Recommended to screen yearly in most patients and in some high risk patients, every 3-6 months by dermatology.
  – Minimize sun exposure and use UV blocking agents.

• Consider switching immunosuppression or decreasing immunosuppression
  – Reduction in Trough goal, and MMF dosing
  – Switching CNI to Rapamune (Sirolimus)
PTLD

- Post Transplant Lymphoproliferative disease
  - Lymphoid and/or plasmacytic proliferations related to immunosuppression that can occur in transplant patients.
  - Most common malignancy after skin cancer in solid organ transplants
  - Usually EBV+ [most common in EBV-(R)/EBV+(D)]
  - Related to B-cell proliferation induced by EBV infection.
  - Host derived (multisystem) or donor derived (allograft)
PTLD Treatment

• Reduction in Immunosuppression
  – Stop Mycophenolate
  – Decrease trough Prograf levels
  – Consider switching Prograf to Sirolimus

• Referral to Hematology-Oncology

• If lesion is Cd20+ → Rituximab

• Chemotherapy (EPOCH)

• In certain cases: Surgery, XRT
Immunosuppression
Clinical Question #1

• 48 year old patient with ESRD due to DM s/p DDRT in October 2017 presents with nausea, vomiting, diarrhea. Post transplantation, the patient has had recent BK Viremia, which has now resolved. CMV has remained negative post transplantation. No history of rejection. Baseline creatinine in the 1.3-1.5 range. Patient is on Prograf, MMF, and Prednisone.
Question

- Which of the following most likely explains the patients presentation to the hospital?

1) Patient with acute rejection
2) Patient had recent MMF dose increased and is now having side effects
3) Patient has new onset CMV colitis
4) Patient has C. Difficile infection
Question

Which of the following most likely explains the patient's presentation to the hospital?

1) Patient with acute rejection
2) Patient had recent MMF dose increased and is now having side effects
3) Patient has new onset CMV colitis
4) Patient has C. Difficile infection
## Phases of Immunosuppression

<table>
<thead>
<tr>
<th>Phase</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Prevent acute rejection during the early posttransplantation period by providing a high degree of immunosuppression at the time of transplantation.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Therapy with a combination of low doses of drugs with non-overlapping toxicities to prevent rejection of the allograft.</td>
</tr>
<tr>
<td>Anti-Rejection</td>
<td>High degree of immunosuppression to treat an ongoing rejection episode.</td>
</tr>
</tbody>
</table>
Three Signal Hypothesis: T-Cell Activation
3 Signal Activity Sites for T-Cell Activation

• SIGNAL 1 – Antigen Recognition and Target
  – Potent inactivation of both naïve and memory T Cells.
  – Inhibition eliminates Antigen Recognition/Specificity

• SIGNAL 2 – Co-Stimulatory Signals
  – Preserves Specificity
  – Limited impact on Memory T Cells

• SIGNAL 3 – Cytokine Signaling and Proliferation
  – Prevents Amplification
  – Blocks later steps in T-Cell Activation
List of Immunosuppressive Medications
Induction Agents

• Polyclonal Antibodies
  – Rabbit anti-thymocyte globulin (Thymoglobulin)
  – Equine anti-thymocyte globulin (ATGAM)

• IL-2a Receptor Antagonists
  – Basilixumab (Simulect)
  – Dacliizumab (Zenapax) – discontinued in the US

• Biologic Agents
  – Alemtuzumab (Campath)
## Maintenance Agents

<table>
<thead>
<tr>
<th>CLASS</th>
<th>AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids (CS)</td>
<td>Methylprednisolone (<em>Solumedrol®</em>)</td>
</tr>
<tr>
<td></td>
<td>Prednisone (<em>Deltasone®</em>)</td>
</tr>
<tr>
<td>Calcineurin Inhibitors (CNI)</td>
<td>Cyclosporine (<em>Neoral®, Sandimmune®, Gengraf, CSA</em>)</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus (<em>Prograf®, FK506, Astagraf XL®</em>)</td>
</tr>
<tr>
<td>Anti-Metabolites</td>
<td>Azathioprine (<em>Imuran®</em>)</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofetil (<em>CellCept®, MMF</em>)</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate sodium (<em>Myfortic®, MPS</em>)</td>
</tr>
<tr>
<td>m-TOR inhibitors (mammalian target of rapamycin)</td>
<td>Sirolimus (<em>Rapamune®</em>)</td>
</tr>
<tr>
<td></td>
<td>Everolimus (<em>Zortress®</em>)</td>
</tr>
<tr>
<td>Selective costimulation blocker</td>
<td>*Belatacept (<em>Nulojix®</em>)</td>
</tr>
</tbody>
</table>
Immunosuppression Summary

- **Induction Agents**
  - **Thymoglobulin**
    - Rabbit antithymocyte globulin
  - **Basilixumab (Simulect)**
    - Chimeric mouse-human Ab (CD-25) of IL-2
  - **High dose steroids (tapered)**

- **Maintenance Agents**
  - **Calcineurin Inhibitors: Tacrolimus** or Cyclosporine
  - **Anti-metabolite: Mycophenolate** or Azathioprine
  - **Steroids: Prednisone**
  - mTOR inhibitors: Sirolimus, Everolimus
  - **Belatacept (newer medication)** – CD80/86 antagonist
    - Used in place of Tacrolimus or Cyclosporine
## Tacrolimus Dosing

- **General Guidelines to Tacrolimus Dosing**

<table>
<thead>
<tr>
<th>Months After Transplant</th>
<th>Tacrolimus Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 months</td>
<td>8-12 ng/ml</td>
</tr>
<tr>
<td>3-6 months</td>
<td>7-9 ng/ml</td>
</tr>
<tr>
<td>6-12 months</td>
<td>5-8 ng/ml</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>4-7 ng/ml</td>
</tr>
</tbody>
</table>
Tacrolimus Pharmacology

• Decreased absorption with food (by up to 1/3)
• T half life – 11.3 hours
• Check TROUGH LEVELS every morning for Inpatient Kidney Transplant Patients. (~7am)
• Dosing: 0.1-0.2 mg/kg/day divided in BID
• IV conversion- 1/3-1/5 of PO dose of 24 hours
# CNI Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Mechanism of Action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin inhibitor</td>
<td>NODAT (33%) Tremor/Insomnia Type 4 RTA, Renal magnesium wasting Hair loss Drug induced TMA CNI renal toxicity</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Calcineurin inhibitor</td>
<td>NODAT (20%) Salt sensitive hypertension Hypercholesterolemia Gingival Hyperplasia, Hirsuitism Drug induced TMA CNI renal toxicity</td>
</tr>
</tbody>
</table>
Sirolimus
Adverse Effects

- Anemia
  - ↑ incidence in combination with Cellcept
- Hyperlipidemia (hypertriglyceridemia): incidence > 50% of pts
- Thrombocytopenia
- Leukopenia
- Impaired wound healing
- Lymphocele/Lymphedema
- Mouth ulcers
- Bone pain
- Diarrhea
- Hepatic artery thrombosis in liver transplants
- Bronchial anastomotic dehiscence in lung transplants
Mycophenolate Mofetil

- **Adverse Events**
  - GI Intolerance – nausea/vomiting, diarrhea
  - Headache
  - Leukopenia/Cytopenia
  - Chills

- **Drug Interaction**
  - Agents interfering with enterohepatic recirculation (CsA)
  - Absorption decreased by presence cholestryramine
  - Aluminum and magnesium containing antacids.
  - Dose reductions for leukopenia
Corticosteroids Adverse Events

• Neurological
  – Psychosis, depression, euphoria
  – Seizures
  – Increased intracranial pressure

• Gastrointestinal
  – Peptic ulcer disease, pancreatitis

• Musculoskeletal
  – Myopathy
  – Osteoporosis, aseptic necrosis

• Skin
  – Poor wound healing
  – Acne, hirsutism

• Ocular
  – Increase intraocular pressure
  – Cataracts/Glaucoma
Belatacept: Selective and Potent Immunosuppression Via Co-Stimulatory Blockade
Advantages of Belatacept

• Can potentially offer improved compliance
• No monitoring of drug levels, which save laboratory and staff time.
• Improved graft survival compared to CsA
• Improved renal function at 7 years compared to CsA.
Other Immunosuppressive Agents

• **IVIG**
  – Desensitization
  – Decrease DSA
  – Antibody mediated rejection

• **Eculizumab (Solaris)**
  – Humanized monoclonal Ab (anti-CD25)
  – Complement inhibition
  – Atypical HUS
  – Antibody Mediated Rejection, and potentially Induciton
  – One of the most expensive drugs

• **Bortezimab (Velcade)**
  – proteasome inhibitor
  – Antibody mediated rejection

• **Rituximab**
  – Monoclonal Ab which Deplete CD20 cells on surface of B-cells.
  – Antibody Mediated Rejection
  – Recurrent FSGS
  – Recurrent Membranous Nephropathy
VACCINATIONS

• SIMPLE RULE OF THUMB:

“Do NOT give patients LIVE or LIVE ATTENUATED VACCINES after transplantation”
LIST OF NO-NOs

• Do Not Give these:
  – Varicella Zoster
  – Intranasal Influenza
  – Bacillus Calmette-Guerin (BCG)
  – Live oral typhoid
  – Measles
  – Mumps
  – Rubella
  – Oral polio
  – Live Japanese B encephalitis vaccine
  – Yellow fever
  – Smallpox
Vaccinations That Are OK

• Okay to give INACTIVATED vaccines.
  – Influenza (type A and B) – yearly
  – Pneumovax (Prevnar-13)– every 3-5 years
  – Haemophilus influenza B
  – Hepatitis B
  – Typhoid Vi
  – Inactivated polio
  – Meningococcus
  – Hepatitis A
DRUG-DRUG INTERACTIONS
<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP2E1</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol</td>
<td>Diclofenac</td>
<td>Diazepam</td>
<td>Amitriptyline</td>
<td>Tylenol</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Fluvastatin</td>
<td>Ibuprofen</td>
<td>Codeine</td>
<td>Ethanol</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Phenytoin</td>
<td>Mephenytoin</td>
<td>Flecainide</td>
<td>Halothane</td>
<td>Clarithromycin</td>
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<tr>
<td></td>
<td>Tolbutamidine</td>
<td>Omeprazole</td>
<td>Imipramine</td>
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<tr>
<td></td>
<td>Warfarin</td>
<td>Phenytoin</td>
<td>Metoprolol</td>
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<td>Diltiazem</td>
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<td></td>
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<td>Proguanyl</td>
<td>Nortriptyline</td>
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<td>Erythromycin</td>
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<td></td>
<td></td>
<td></td>
<td>Propafenone</td>
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<td>Everolimus</td>
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<td></td>
<td></td>
<td></td>
<td>Propafenone</td>
<td></td>
<td>Itraconazole</td>
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<td></td>
<td></td>
<td></td>
<td>Propanolol</td>
<td></td>
<td>Ketoconazole</td>
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<td></td>
<td></td>
<td></td>
<td>Thioridazine</td>
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<td>Lovastatin</td>
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<td></td>
<td></td>
<td></td>
<td>Timolol</td>
<td></td>
<td>Midazolam</td>
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<td></td>
<td></td>
<td></td>
<td>Nefazodone</td>
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<td></td>
<td></td>
<td></td>
<td>Nifedipine</td>
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<td></td>
<td></td>
<td>Protease Inhib.</td>
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<td></td>
<td></td>
<td></td>
<td>Quinidine</td>
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<td></td>
<td></td>
<td></td>
<td>Sildenafil</td>
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<td></td>
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<td>Simvastatin</td>
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<td></td>
<td></td>
<td></td>
<td>Sirolimus</td>
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<td>Tacrolimus</td>
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<td>Terbinafine</td>
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<td>Verapamil</td>
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<td>Warfarin</td>
</tr>
</tbody>
</table>

**CYTOCHROME P450 ISOENZYMES**

Metabolize many clinically relevant drugs

- Tylenol
- Ethanol
- Halothane
- Diazepam
- Ibuprofen
- Mephenytoin
- Omeprazole
- Phenytoin
- Proguanyl
- Amitriptyline
- Codeine
- Flecainide
- Imipramine
- Metoprolol
- Nortriptyline
- Propafenone
- Propanolol
- Thioridazine
- Timolol
- Amiodarone
- Atorvastatin
- Clarithromycin
- Cyclosporine
- Diltiazem
- Erythromycin
- Everolimus
- Itraconazole
- Ketoconazole
- Lovastatin
- Midazolam
- Nefazodone
- Nifedipine
- Protease Inhib.
- Quinidine
- Sildenafil
- Simvastatin
- Sirolimus
-Tacrolimus
- Terbinafine
- Verapamil
- Warfarin
## CYP3A4 Inhibitors (increase level)

<table>
<thead>
<tr>
<th>Class</th>
<th>Inhibiting Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibacterial (macrolide)</td>
<td>Clarithroymycin, Erythromycin</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Fluvoxamine, Nefazodone</td>
</tr>
<tr>
<td>Azole Antifungals</td>
<td>Fluconazole, Voriconazole, Itraconazole etc</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Diltiazem, Verapamil</td>
</tr>
<tr>
<td>Foods</td>
<td>Grapefruit, pomegranate</td>
</tr>
<tr>
<td>Protease Inhibitors (Hep C)</td>
<td>Boceprevir, Telaprevir</td>
</tr>
<tr>
<td>Protease Inhibitors (HIV)</td>
<td>Atazanavir, darunavir, Fosamprenavir, indinavir, Nelfinavir, ritonavir, saquinavir</td>
</tr>
<tr>
<td>Others</td>
<td>Amiodarone, Dalfopristin</td>
</tr>
<tr>
<td>Statins</td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>
# CYP3A4 Inducers (Lower drug levels)

<table>
<thead>
<tr>
<th>Class</th>
<th>Inducing Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseizure Medications</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Fosphenytoin</td>
</tr>
<tr>
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<td>Oxcarbazepine</td>
</tr>
<tr>
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<td>Phenobarbital</td>
</tr>
<tr>
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<td>Phenytoin</td>
</tr>
<tr>
<td>Anittuberculosis</td>
<td>Rifabutin</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Others</td>
<td>Bosentin</td>
</tr>
<tr>
<td></td>
<td>Modafanil</td>
</tr>
<tr>
<td></td>
<td>St. John Wort</td>
</tr>
</tbody>
</table>
Summary

• Kidney transplant is the treatment of choice in terms of renal replacement therapy for a majority of ESRD patients.

• Multi-disciplinary approach

• Check Tacrolimus Trough levels every morning (around 7am) for all Inpatient Kidney Transplant patients.

• Only Inactivated Vaccines are okay after transplant.

• Increased comfort level in dealing with kidney transplant patients, their immunosuppression, and common post transplant management issues.