The Pharmacist Role in Organ Transplantation:

Optimizing Safety & Efficacy

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Objectives

PHARMACIST

- Describe mechanisms of transplant immunosuppression
- Identify common adverse effects to transplant immunosuppression
- Modify transplant regimens to ensure safety and efficacy

TECHNICIAN

- List medications used in transplant recipients
- Outline documentation requirements for transplant medications

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Epidemiology – U.S.

At a Glance

113,250
people need lifesaving kidney transplants (total waitlist candidates)
As of 6/12/19

16,165
transplants have been performed this year (January to May 2019)

7,740
donors recovered so far in 2019

Every ten minutes, someone is added to the national transplant waiting list.

On average, 22 people die each day while waiting for a transplant.

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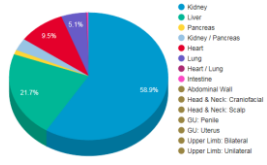
Epidemiology – U.S.

Transplants By Organ Type January 1, 1988 - May 31, 2019 Based on OPTN data as of June 11, 2019



2018 transplants by organ type

- Kidney 21,167
- Pancreas 192
- Liver 8,250
- Intestine 104
- Heart 3,408
- Heart/lung 32
- Lung 2,530
- VCA
- Vascular allograft (VCA) 11
- Kidney/ Pancreas 836

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Epidemiology – New Mexico

At a Glance

553
people need lifesaving kidney transplants in New Mexico

49
kidney transplants have been performed in New Mexico (January to May 2019)

2,380
Patients have been transplanted since 1988

DONATE LIFE New Mexico

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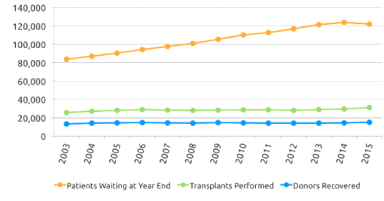
Epidemiology

The need continues to grow



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Indications for Transplant

Modifiable	• Diabetes • Hypertension • Obesity • Substance Overuse (NSAID, APAP, EtOH) • Smoking
Non-Modifiable	• Genetics • Congenital Abnormalities • Autoimmune Disorders

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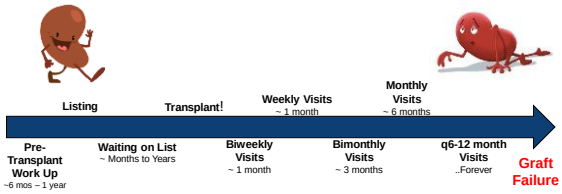
Transplant Course



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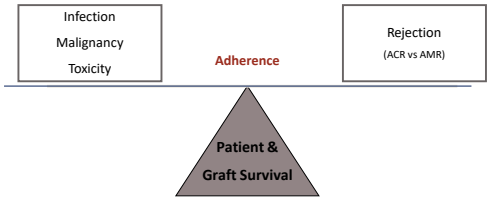
Goals of Immunosuppression



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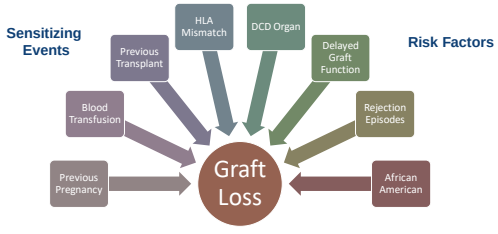
Sensitization & Risk Factors for Rejection



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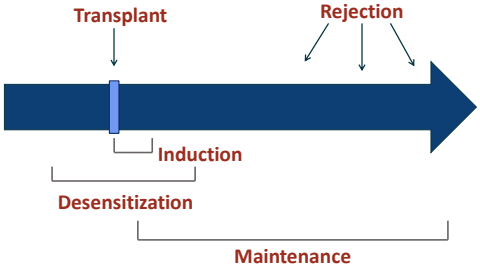
Phases of Immunosuppression



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Determination of Regimens

- **Evaluation of Immunologic Risk**
  - HLA mismatch
  - Younger recipient and older donor
  - African-American
  - Panel Reactive Antibody (PRA) > 0
  - Donor-specific Antibody (DSA)
  - Blood group incompatibility
  - Delayed onset of graft function (DGF)
  - Cold ischemia time > 24 hours
- **Evaluation of Infectious Risk**
  - Elderly
  - HBV exposure
  - HCV exposure
  - Previous chemotherapy
  - ganR CMV

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Induction Agents

Goal: *To prevent early acute allograft rejection immediately post-transplant using intense, prophylactic immunosuppressive therapy*

- **Basiliximab (Simulect®)**
  - 20 mg IV POD0 and POD4
- **Antithymocyte Globulin (Thymoglobulin®)**
  - 2 mg/kg (IBW) IV starting POD0 up to 6mg/kg total
  - Dosing regimens vary based on center
- **Alemtuzumab (Campath®)**
  - 30 mg IV POD0

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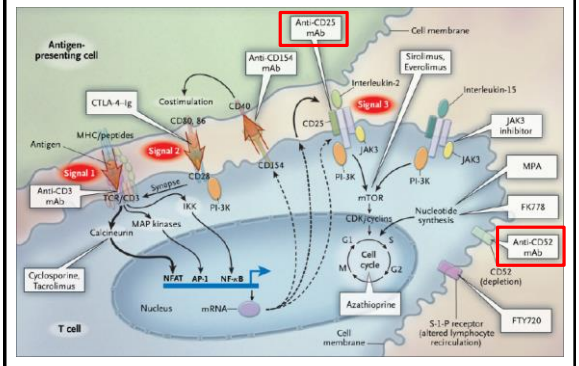

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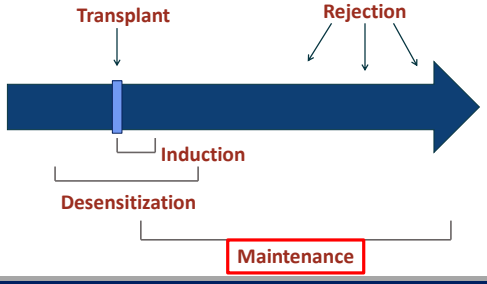
Phases of Immunosuppression



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Maintenance Agents

Goal: *To prevent early and late allograft rejection post-transplant using long-term prophylactic immunosuppressive therapy*

- **Corticosteroids** (Methylprednisolone, Prednisone)
- **Calcineurin Inhibitors** (Tacrolimus, Cyclosporine)
- **Antimetabolites** (Mycophenolate, Azathioprine)
- **CTLA-4 Blockade** (Belatacept)
- **mTOR Inhibitors** (Sirolimus, Everolimus)

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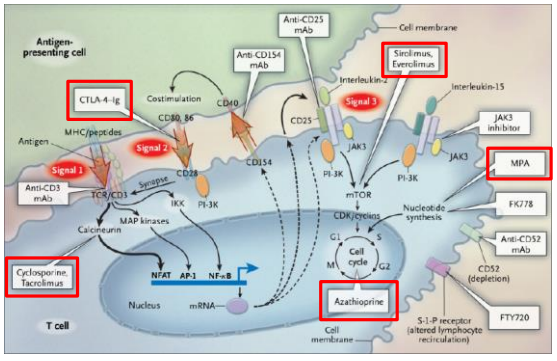

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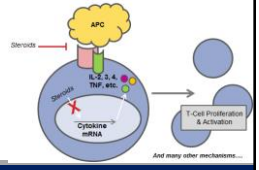
Corticosteroids (Prednisone, Methylprednisolone)

- **Mechanism of Action:**
  - Profound immune system augmentation including inhibition of IL-1, 2, 3, 4, 5, 6, 8, TNF involved in **T-cell proliferation**; decreased **B-cell clone expansion**, and decreased antibody synthesis
- Increased risk of bacterial, mycobacterial, viral and fungal infections
- Routinely used to treat rejection



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Corticosteroids (Prednisone, Methylprednisolone)

- **Adverse Effects**..... *are plenty*

SHORT TERM
- Mood Change
- Hyperglycemia*
- Hypertension*
- Increased Appetite
- Insomnia
- Acne
- Leukocytosis*

LONG TERM
- Osteoporosis
- Adrenal Insufficiency
- Ulcerative Esophagitis
- Hirsutism
- Pacreatitis
- Amenorrhea
- Diabetes Mellitus

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Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

PROGRAF (tacrolimus)

Neoral (cyclosporine capsules, USP) MODIFIED

GENGRAF (cyclosporine capsules, USP) MODIFIED

Once-daily Envarsus XR (tacrolimus extended-release tablets)

SANDIMMUNE Soft Gelatin Capsules (cyclosporine capsules, USP)

ASTAGRAF XL (tacrolimus extended-release capsules)

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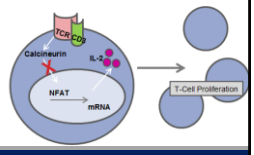
Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

- **Mechanism of Action:**
  - Binds to immunophilins and block the function of calcineurin at different enzymatic sites, resulting in downstream impairment of **T-cell** IL-2 synthesis
- Tacrolimus is broader in inhibitory effect (IL-3, IL-4, IL-5, IFN-γ, other cytokines)
- CsA has antiviral properties
  - HIV, HSV, HCV
- Increased risk of CMV and BKV



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Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

- **Drug Interactions**
  - *Primarily through hepatic metabolism (CYP3A4 inhibition or induction)*
    - ↑ **Drug Level:** ketoconazole, diltiazem, fluconazole, grapefruit juice
    - ↓ **Drug Level:** phenytoin, rifampin
  - P-gp Substrate
  - Drug interactions have high inter- and intra-patient variability
  - Consistent administration with or without food

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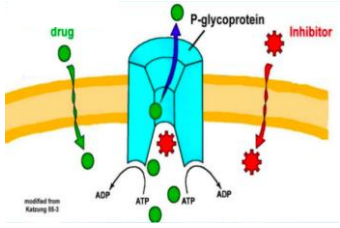
Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

GUT



BLOOD

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When to Check Troughs?

- Depends on the clinical situation and **when last trough was checked**
- Recommend **erring on side of caution** and checking a trough when in doubt
- Any AKI
  - Tacrolimus can be the cause of AKI
  - Tacrolimus is NOT renally excreted
- Any diarrhea
  - Tacrolimus levels are **increased during episodes of diarrhea**

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Tacrolimus Preparations

- **Prograf**
  - Immediate release **capsule**
  - IV preparation
    - Dose reduce to 1/3 of oral dose as a continuous infusion
    - Please don't do this – use sublingual instead (if possible)
  - Can be used for SL administration
    - Dose reduce 1 mg PO : 0.5 mg SL
- **Astagraf**
  - Once-daily long-acting **capsule**
  - Really only used for tacrolimus-sensitive patients (ie, 0.5mg once a day = 0.25mg Prograf BID)

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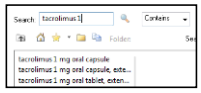
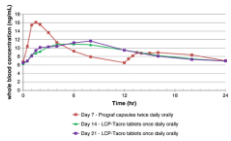
Tacrolimus Preparations

- **Envarsus XR**
  - Once-daily long-acting **tablet**
  - Fantastic pharmacokinetics!
  - Significantly less neurotoxicity





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Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

- **Tacrolimus Adverse Effects**

- Hypertension
- Diarrhea
- Nephrotoxicity
- Headache
- Hepatotoxicity
- Neurotoxicity

- Hyperglycemia*
- Pruritis
- Hyperkalemia
- Hypomagnesemia
- Infection
- Alopecia

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Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

- **Cyclosporine Adverse Effects**

LESS COMMON
- Migraine
- Acne
- GI effects
- Gynecomastia
- Hyperkalemia
- Hypomagnesemia
- Hepatotoxicity

MORE COMMON
- Hyperlipidemia
- Nephrotoxicity
- Tremor
- Hypertension
- Hyperglycemia
- Gingival hyperplasia
- Hirsutism

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Calcineurin Inhibitors (Tacrolimus, Cyclosporine)

- **Adverse Effects**

	Tacrolimus	Cyclosporine
Nephrotoxicity	+++	++
Hyperglycemia & DM	+++	++
Neurotoxicity	+++	++
Electrolyte abnormalities	+++	++
Hypertension	+++	+++
Other	Alopecia	Hirsutism, hyperlipidemia, gingival hyperplasia, hyperuricemia

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Time to Panic! We are Entering a Generic Tacrolimus Shortage…

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Tacrolimus Shortage

- Announced by FDA on 5/17/19
  - Expected to last ~12 months
  - Due to raw materials shortage
- Currently only affects generic formulations
- Drug is being allocated
  - UNMH is actively converting people to Astagraf and Envarsus preparations
- Conversion to other preparations in non-kidney transplant can be difficult due to insurance
  - Not FDA indicated in lung, liver, or pancreas

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Antimetabolites (Mycophenolate, Azathioprine)

CellCept® mycophenolate mofetil

myfortic® enteric-coated mycophenolate sodium

IMURAN® (AZATHIOPRINE)

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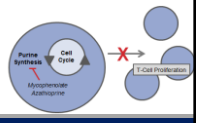
Antimetabolites (Mycophenolate, Azathioprine)

- **Mechanism of Action:**
  - Targets enzymes involved in de novo synthesis of purines leading to impairment of DNA replication in **B- and T-cells**
- Potential for bone marrow suppression
- Significantly increased risk for major viral, fungal and parasitic infections
- Usually the first agent pulled when patient has infection



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Antimetabolites (Mycophenolate, Azathioprine)

- **Mycophenolate Conversion**
  - *Conversion: 180 mg Myfortic = 250 mg CellCept*
- Myfortic is enteric coated for delayed release*
- *Black Box Warning*
- Mycophenolate is teratogenic and cannot be used in pregnancy
- **Azathioprine** is reserved for mycophenolate intolerance or women who want to become pregnant

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Antimetabolites (Mycophenolate, Azathioprine)

- **Drug Interactions**
  - *Primarily through decreased absorption*
    - Cholestyramine, sucralfate
  - ?Cations???
    - Studies show ↓ AUC
    - AUC not well correlated with graft outcomes
    - Missed doses (due to 4x/day dosing regimens) HAVE been correlated with significantly worse outcomes
  - Azathioprine:
    - Mercaptopurine – profound myelosuppression
    - Allopurinol/Febuxostat – profound myelosuppression

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Antimetabolites (Mycophenolate, Azathioprine)

- **Mycophenolate Adverse Effects**
  - **GI Intolerance!!**
    - Diarrhea
    - Nausea
    - Bloating
  - **Bone Marrow Suppression**
    - Leukopenia
    - Neutropenia
    - Thrombocytopenia
  - Back Pain
  - Hyperglycemia

Dose Limiting Adverse Effects!

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Antimetabolites (Mycophenolate, Azathioprine)

- **Azathioprine Adverse Effects**
  - Bone Marrow Suppression
    - Leukopenia
    - Neutropenia
    - Thrombocytopenia
  - Increased LFTs
    - AST, ALT, Alk Phos, Tbili
  - Myalgias
  - GI Intolerance

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CTLA-4 Inhibitors (Belatacept)

Nulojix (belatacept)

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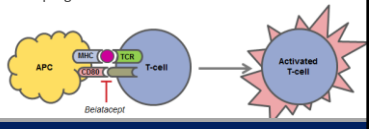
CTLA-4 Inhibitors (Belatacept)

- **Mechanism of Action:**
  - Binds CD80 and CD86 receptors on APCs to block selective **T-cell** costimulation leading to lack of response by T-cell
- Risk of PTLD in EBV seronegative recipients
- Non-standard maintenance agent used to preserve renal function
- Part of a limited-distribution program



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CTLA-4 Inhibitors (Belatacept)

- **Adverse Effects**

Black Box Warning

  - Post-Transplant Lymphoproliferative Disorder (PTLD)
    - Must be **EBV seropositive** to receive medication
  - GI Disturbances
  - Hypertension
  - Peripheral Edema
  - Anemia

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mTOR Inhibitors (Sirolimus, Everolimus)

Rapamune sirolimus 0.5 mg, 1 mg, 2 mg Tablets

ZORTRESS® (everolimus) Tablets 0.25 mg, 0.5 mg, 0.75 mg

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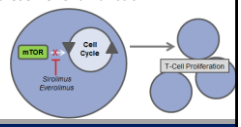
mTOR Inhibitors (Sirolimus, Everolimus)

- **Mechanism of Action:**
  - Binds mTOR inhibiting pathways needed for mRNA translation critical for cell division in **T- and B-cells**
- Antiviral properties
- Decreased wound healing due to inhibition of fibroblasts
- Non-standard maintenance agent used to preserve renal function



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mTOR Inhibitors (Sirolimus, Everolimus)

- **Adverse Effects**
  - Edema
  - Anemia
  - Impaired Wound Healing
  - Interstitial Lung Disease*
  - Proteinuria
  - Hyperlipidemia

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Practical Considerations for Maintenance Medications

- Do not need to separate from cations (calcium, magnesium, iron, etc)
  - Theoretical interaction, decreases compliance
- Take consistently with regards to food
  - Taking with food reduces nausea
  - Fat content should be similar between meals
- Do not hesitate to check a CNI/mTORi trough if worried about under- or over-dosing, or patient has symptoms

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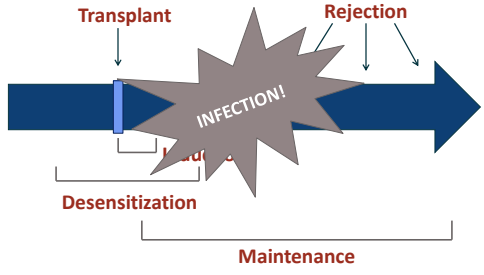
Phases of Immunosuppression



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Infectious Complications

- Temporally distributed
- Immunosuppressive regimen
  - Dose, duration, sequence
- Comorbid conditions
  - Diabetes, malnutrition, neutropenia, alcoholic cirrhosis, autoimmune diseases, etc
- Immunomodulating viral infections
  - CMV, EBV, HBV, HCV, HHV6
- Presence of foreign material
  - Intravenous catheters, foleys, etc

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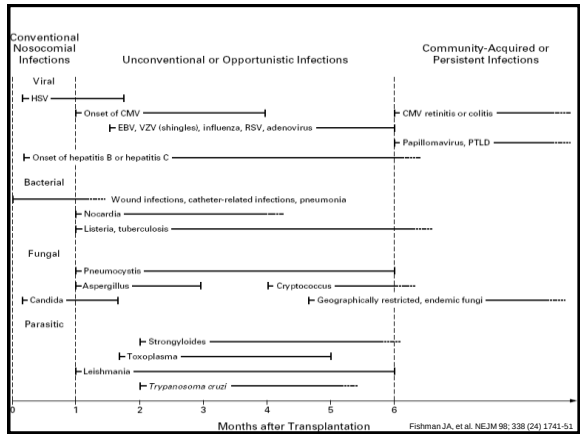

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Infection Prophylaxis

Bactrim	Valganciclovir	Oral Nystatin Or Azole*
Pneumocystis UTI Pathogens	Cytomegalovirus Herpes Simplex Varicella Zoster	Oropharyngeal Candida Invasive Fungal Infections*

Day 0 = Day of Transplant

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Infection Prophylaxis

- Resumed when patient is treated for rejection
- Oftentimes have specific stop dates
- Can drive drug resistance
  - Transplant antibiograms are different than general population

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Rejection

- **Acute Cellular Rejection**
  - T-Cell Mediated
  - Relatively Common
  - Easily Treated
- **Antibody Mediated Rejection**
  - Difficult to Treat
  - Usually Related to Non-Adherence
- **Chronic Rejection**
  - No Treatment
  - Slow Progression to Graft Failure

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Malignancy

- **Related to degree of immunosuppression**
  - Increased risk with increased survival
- Lung, breast, colon, and prostate cancer are not increased compared to general population
- Increased risk of lymphomas and lymphoproliferative disorders, Kaposi's sarcoma, renal carcinoma, and skin cancers

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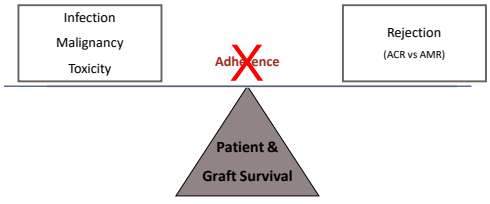
Goals of Immunosuppression



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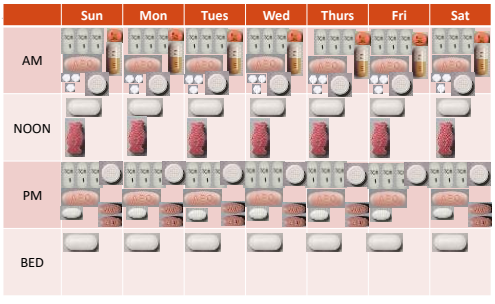
Weekly Pill Box Post-Transplant



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Barriers to Adherence

- **S**ystem
  - Prior authorizations, transportation
- **M**otivation
  - Depression, feeling "different"
- **U**nderstanding
  - Education level, language barriers
- **R**ecall
  - Variable schedule, distractions
- **F**inancial
  - Cost of medications

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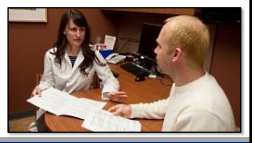
Barriers to Adherence

- **PHARMACISTS** are the best provider to address adherence
- As drug experts, it is our duty to own the entire process of medication use
- If you see something abnormal, contact the transplant team! We love fixing issues



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Barriers to Adherence

- **SEE SOMETHING, SAY SOMETHING!!**
- Many patients never notify their transplant clinic of issues with medications
- Increases risk for non-adherence, rejection, and poor outcomes
- Community Pharmacists are our eyes and ears
  - Let us know what's going on!
  - We are always happy to help

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Transplant Medication Billing

- Complicated!
  - Non-kidney transplants are billed through private insurance or patient's Medicare if they qualify for Medicare based on age, disability
- Depends on patient insurance and Medicare status at time of transplant
- Requires specialized knowledge and infrastructure to bill for medications
- Can really mess up a patient's insurance situation if not billed correctly
  - Put someone in the donut hole ☹

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Transplant Medication Billing (Kidney)

On Medicare at Time of Transplant (≥65 yo)

- Immunosuppressants billed through Medicare B and 80% is covered
- Remaining 20% is billed through Medicare B supplement
- Patient has $0 copay for immunos
- No prior authorizations needed
- Eligible to bill immunos through Med B forever

On Medicare at Time of Transplant (< 65 yo)

- Receives Medicare B for 3 years post-transplant
- At 3 years, patient loses Med B *unless* they have another reason for disability
- Patient's drug plan is now responsible for immunos
- Prior authorizations usually needed
- Copays dictated by insurance carrier

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Transplant Medication Billing (Kidney)

No Medicare at Time of Transplant

- Immunosuppressants billed through prescription drug plan (Medicaid, NMMIP, private, etc)
- Prior authorizations usually needed
- Copays dictated by insurance carrier

If billing Medicare You Need:

- ICD10 Code: Z94.0
- Transplant Date
- Discharge Date
- Cannot be for >30 Day Supply
- Cannot be on Automatic Refill

…You could get audited

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Limitations in Transplant

- Every center **practices differently**
- Most evidence based on **retrospective, single-center experiences**
- Many medications are used **"off-label"**

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Summary

- Immunosuppression is **complex** and **patient specific**
- Transplant providers and pharmacists **work together** to create the most balanced regimen possible
- Protocolization provides a framework for patient management, but **doesn't fit every patient**
- Transplant clinics and community pharmacies **must work together** to provide the best care possible for this high risk, high cost patient population
- **Understanding and appropriately billing** transplant medications ensures there are no gaps in care

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References

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Questions?

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