Kidney Transplantation: Focus on Pharmacotherapy

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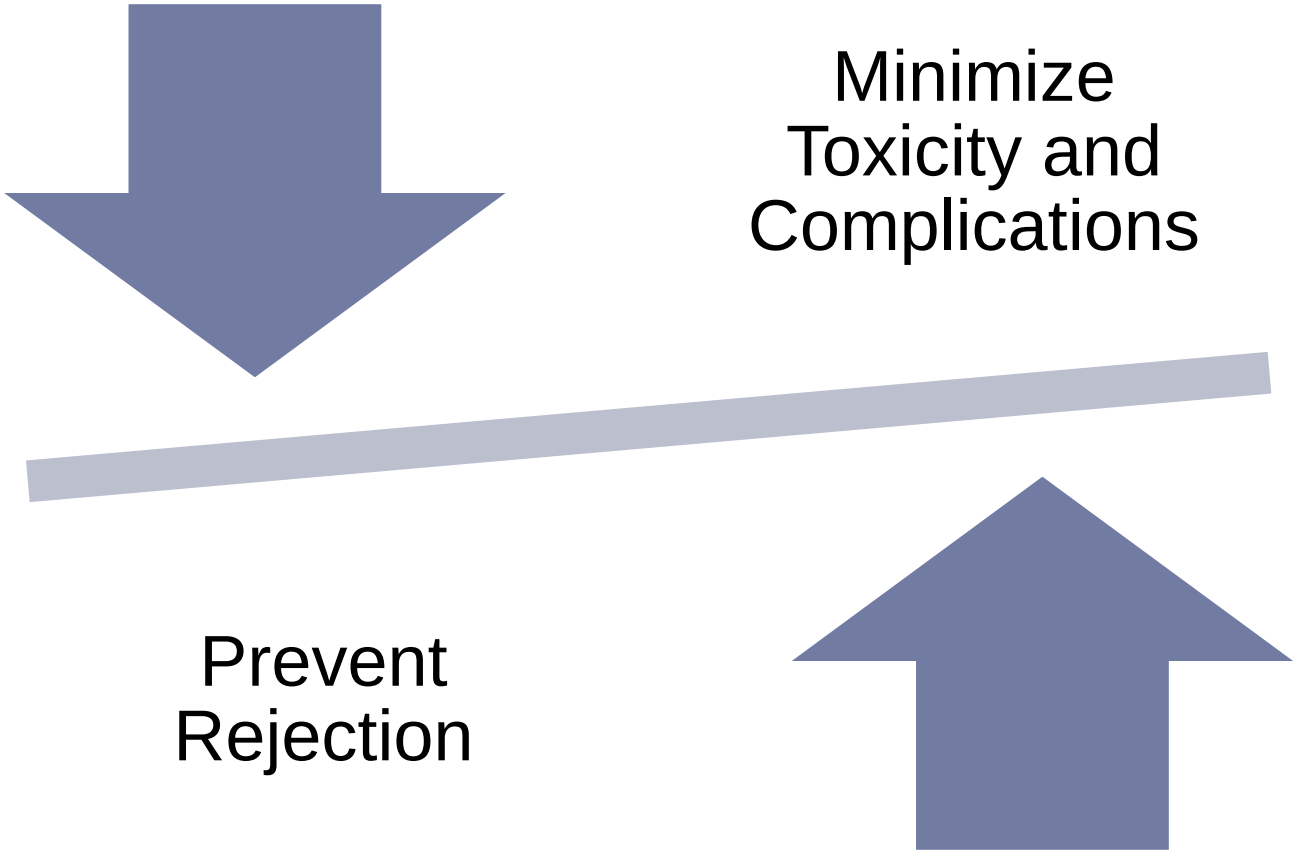
Objectives

- Review immunosuppressive medications used in kidney transplantation
- Examine adverse effects, drug interactions, and monitoring parameters of these agents
- Interpret therapeutic drug monitoring for immunosuppressants
- Present “clinical pearls” related to medication usage in kidney transplant patients

IMMUNOSUPPRESSION

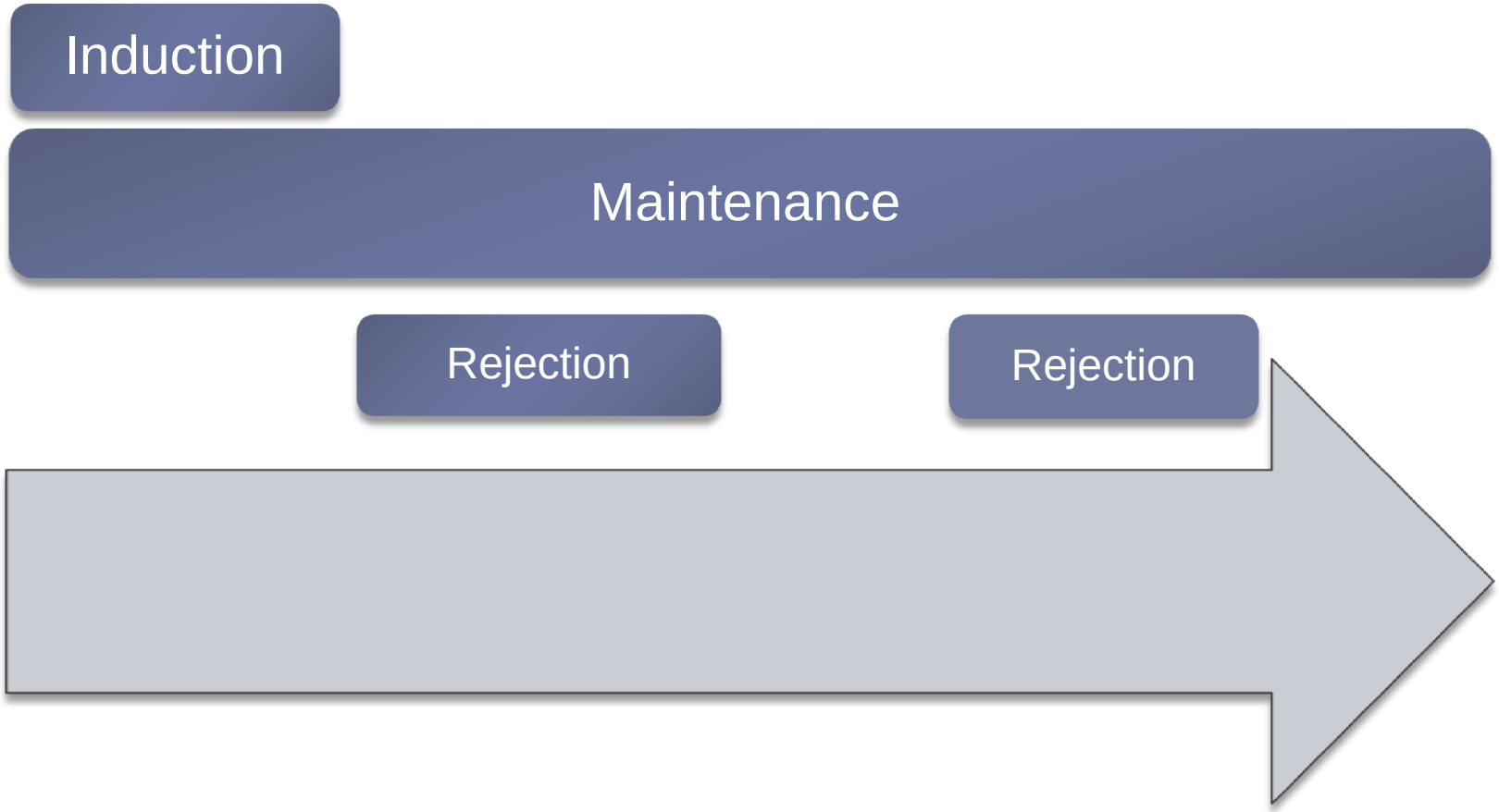
Goals of Immunosuppression



Complications of Immunosuppression

- Infection
- Malignancy
  - Post-transplant lymphoproliferative disorder (PTLD)
  - Skin cancers
- Drug-specific adverse effects

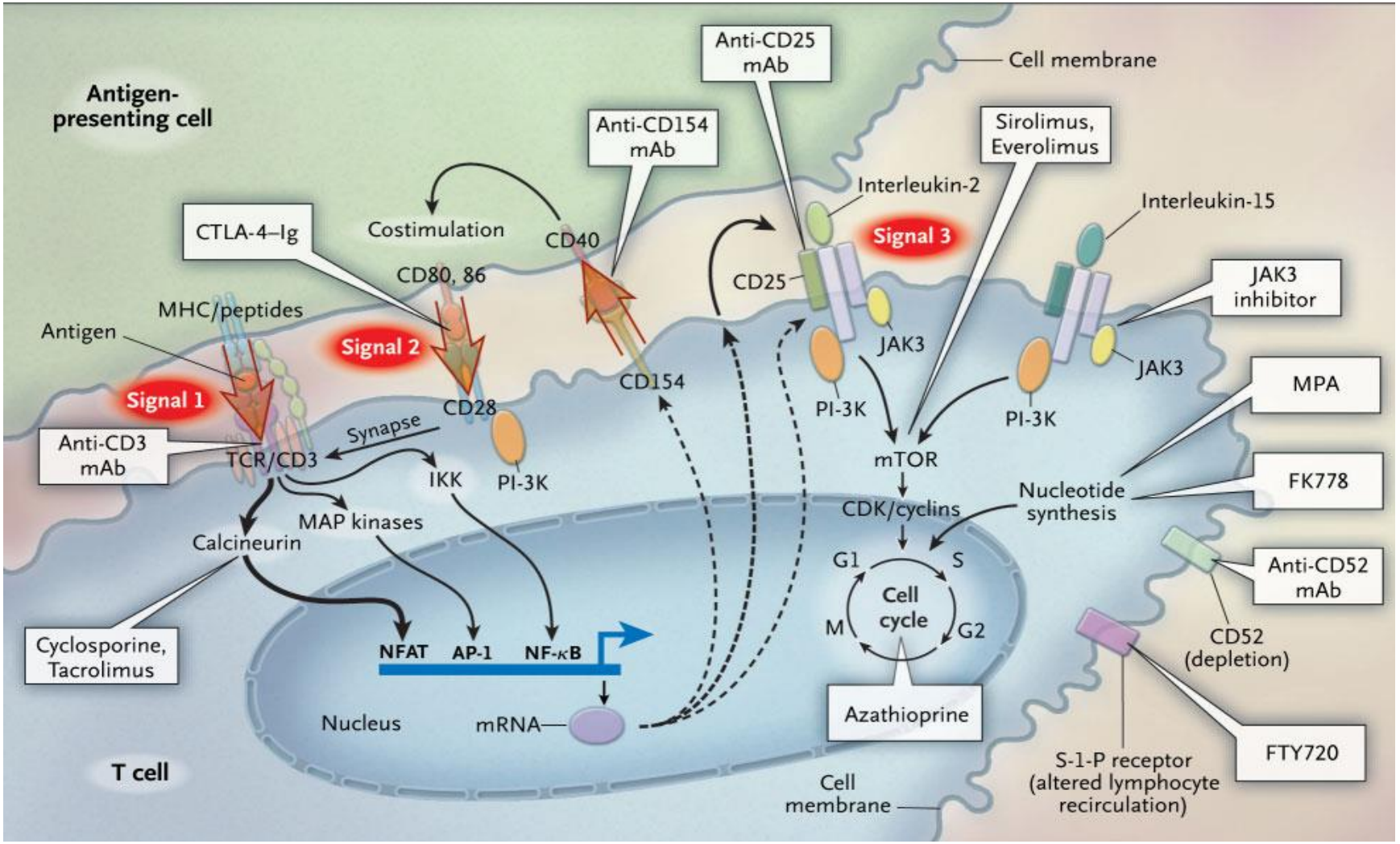
Phases of Immunosuppression



Disclaimer: Gray Areas

- Immunosuppressive protocols are:
  - Organ-specific
    - Eg. Induction therapy is frequently used in kidney transplant but rarely in liver transplant
  - Center-specific
    - Eg. The regimens used for kidney transplant recipients at UCM may be different from those used at Northwestern and Rush
  - Patient-specific
    - Eg. If a patient develops neurotoxicity as a result of tacrolimus, may consider conversion to cyclosporine

Pharmacology of Immunosuppression



Halloran PF. *NEJM* 2004; 351(26): 2715-29.

INDUCTION

Induction

- Initiated prior to or at the time of transplantation
- Results in rapid and prolonged immunosuppression
- Goal is prevention of acute rejection in the early post-transplant period
- Use varies by transplant type and center

Agents Used in Induction

- Non-T-cell depleting
  - Interleukin-2 (IL-2) receptor antagonists
    - Basiliximab (Simulect®)
    - Daclizumab (Zenapax®)*
- T-cell depleting
  - Antithymocyte globulin
    - Rabbit (RATG, Thymoglobulin®)
    - Equine (ATG, ATGAM®)
  - Alemtuzumab (Campath®)
  - Muromomab (OKT3)*

*No longer commercially available

Basiliximab (Simulect®)

- Induction agent
- Mechanism of action: IL-2 receptor (CD25) antagonist
- Dose: 20 mg IV intraoperatively and day 4 post-transplant
  - Reduce dose to 10 mg if patient weighs <35 kg
- Adverse effects: minimal-similar to placebo

Antithymocyte Globulin

- Used for induction and treatment of rejection
- RATG more frequently selected than ATG
- Induction dose (RATG): 1.5 mg/kg IV for 3 to 7 doses
  - Usually given via a central line over 4 to 6 hours
  - Premedicate with APAP, diphenhydramine, and steroids
- Confirm that patient does not have a rabbit allergy
- Adverse effects: infusion-related reactions, leukopenia, thrombocytopenia, infection, malignancy risk
  - Dose adjustments may be needed for leukopenia/thrombocytopenia

RATG Infusion Reactions

- Symptoms: Fever, chills, labile blood pressure, muscle aches
  - Slowing infusion rate may alleviate minor reactions
  - For severe reactions: stop infusion and consider alternate therapies

- Monitoring: Vitals every 15 minutes for first hour of infusion then hourly thereafter

MAINTENANCE IMMUNOSUPPRESSION

Classes of Maintenance Immunosuppressants

- Calcineurin inhibitors (CNIs)
- Antiproliferatives
- Corticosteroids
- mTOR (signal proliferation) inhibitors
- Co-stimulation blocker

Maintenance Immunosuppression

- Typically consists of two to three medications from **different** classes
  - **CNI + antiproliferative +/- steroids**
  - mTOR inhibitor + CNI + steroids
  - mTOR inhibitor + antiproliferative + steroids
  - Co-stimulation blocker + antiproliferative + steroids
- Regimen may be minimized over time
- Note that immunosuppressants are frequently used off-label

Calcineurin Inhibitors (CNIs)

- Cyclosporine (CSA)
- Tacrolimus (TAC, AKA: FK506)

- Mechanism of action: Decrease production of interleukin (IL)-2 and other cytokines to inhibit T cell proliferation
  - Cyclosporine binds to cyclophilin
  - Tacrolimus binds to FK-binding protein

- Pharmacokinetics: CYP3A4 and P-glycoprotein substrates **(=LOTS of drug interactions)**

Tacrolimus (Prograf®, Envarsus XR®, Astagraf XL®)

- Most commonly used CNI
  - Considered more potent than CSA and has largely replaced it in the market
- Usual dose
  - Initial: Patient-specific, typical starting dose is 0.05 mg/kg PO every 12 hours (immediate-release tacrolimus)
  - May delay initiation in the short term post-transplant
  - Titrated to desired goal trough range (eg. 4-12 ng/mL)
- Routes of administration
  - PO: capsules (Prograf/Astagraf 0.5 mg, 1 mg, 5 mg capsules, Envarsus 0.75 mg, 1 mg, 4 mg tablets), suspension (compounded)
  - Sublingual: open capsules and sprinkle contents under tongue
  - IV: **AVOID** if possible

Tacrolimus

- Adverse effects
  - Nephrotoxicity
  - Electrolyte abnormalities (hyperkalemia, hypomagnesemia)
  - Hypertension
  - Hyperlipidemia
  - **Post-transplant diabetes**
  - **Neurotoxicity**
  - **Alopecia**

Cyclosporine (CSA)

- First CNI developed

- Usual dose
  - Initial: patient-specific, typically ~3 mg/kg PO every 12 hours
  - May delay initiation in the short term post-transplant
  - Adjusted to achieve desired goal trough range (eg. 100-300 ng/mL)

- Routes of Administration
  - PO: capsules (25 mg, 100 mg), solution
  - IV: **AVOID** if possible

Cyclosporine

- Adverse effects
  - Nephrotoxicity
  - Electrolyte abnormalities (hyperkalemia, hypomagnesemia)
  - **Hypertension**
  - Hyperlipidemia
  - Post-transplant diabetes
  - Neurotoxicity
  - **Hirsutism**
  - **Gingival hyperplasia**

Cyclosporine Products

- Cyclosporine (Non-Modified)
  - Sandimmune®
  - Cyclosporine USP

- Cyclosporine Modified
  - Neoral®
  - Gengraf® (branded generic)
  - Cyclosporine Modified USP

- **REMEMBER:**
  - Sandimmune® ≠ Neoral®
  - Cyclosporine ≠ Cyclosporine Modified

CNIs: CYP3A4 and P-glycoprotein Drug Interactions

Drugs that DECREASE blood levels of CNIs	Drugs that INCREASE blood levels of CNIs
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Calcium Channel Blockers: Diltiazem Verapamil
Antimicrobials: Rifabutin Rifampin	Antifungals: Voriconazole Posaconazole Itraconazole Ketoconazole Fluconazole
Herbals: St. John's Wort	Macrolides: Clarithromycin Erythromycin
Antiretrovirals: Efavirenz	Others: Amiodarone Protease inhibitors

CNIs: Interactions

- Drug-Disease State Interactions
  - QTc prolongation (especially with TAC)
  - Diarrhea (increases TAC exposure)
  - Liver dysfunction

- Drug-Food Interactions
  - Grapefruit and grapefruit juice (CYP3A4 inhibitor)

CNI-Induced Nephrotoxicity

- Acute
  - Hemodynamically-mediated nephropathy
  - Often exposure-dependent
  - Signs and symptoms include ↑SCr, ↑ BP, ↑ K-may resemble acute rejection
- Chronic
  - May result in irreversible kidney damage

CNIs-Therapeutic Drug Monitoring (TDM)

- Important for evaluating efficacy and toxicity
- 12 hour trough levels are use for immediate-release TAC and CSA, 24 hour troughs for extended-release TAC
- Half-life
  - Tacrolimus ~11 hours
  - Cyclosporine ~19 hours
- Time to achieve steady state ~3-5 half-lives

CNIs-Therapeutic Drug Monitoring (TDM)

- When assessing levels, the following should be taken into consideration:
  - Is it a “true” trough?
  - Goal range (may be per protocol or patient-specific)
  - Serum creatinine trend
  - Previous drug levels (does this level “make sense?”)
  - CNI dose
  - Concomitant medications
    - Prescription, OTC, and herbals
    - New/recently discontinued medications
  - Any complaints of side effects? Evidence of graft dysfunction?
  - Other factors: adherence, diarrhea, drug-food interactions

Antiproliferatives

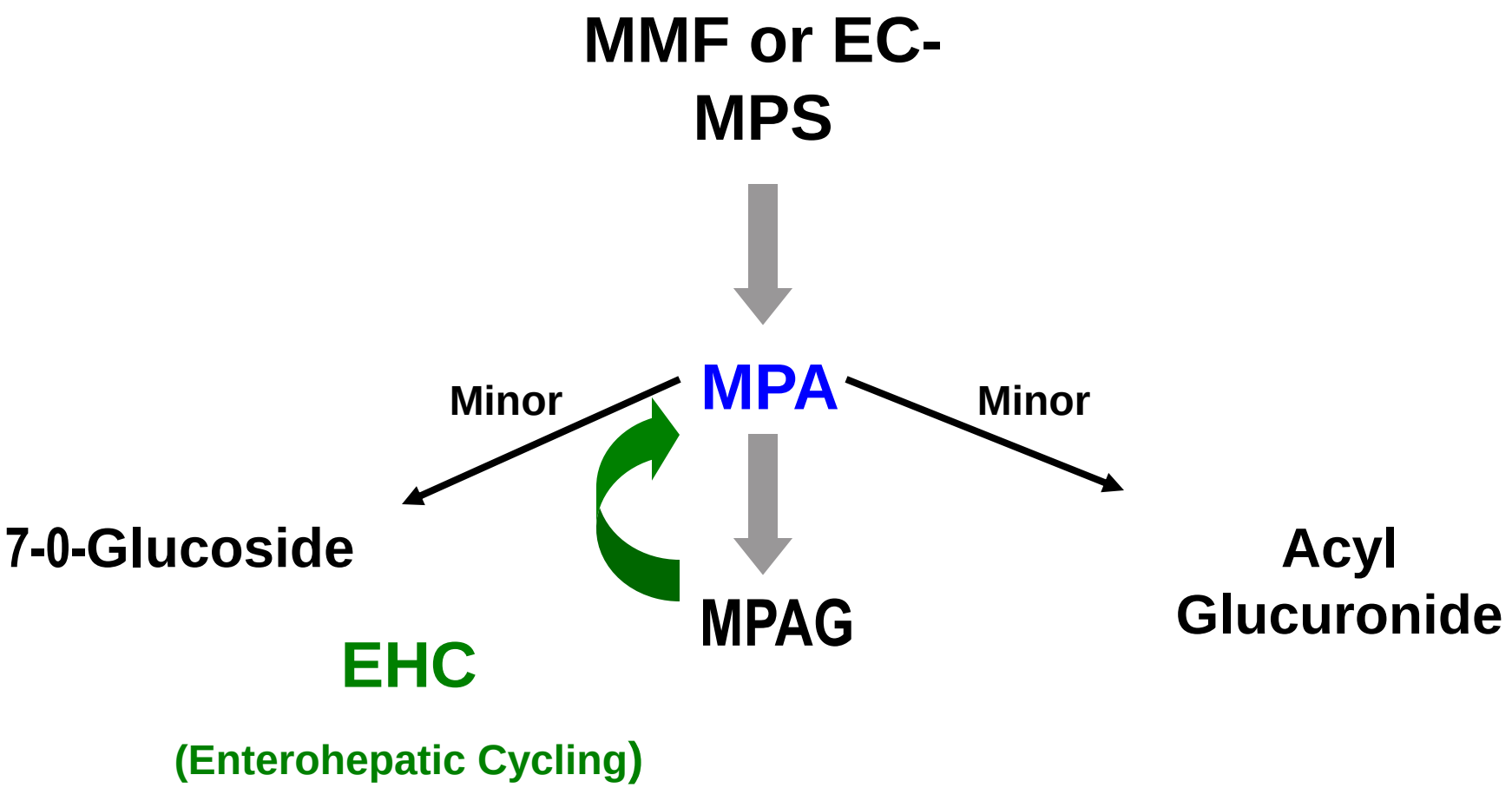
- Mycophenolate products
  - Mycophenolate mofetil (Cellcept®)
  - Mycophenolate sodium (Myfortic®)

- Azathioprine (Imuran®)
  - Largely replaced by mycophenolate
  - May still be preferred agent in select situations
    - GI intolerance to mycophenolate
    - Females who are trying to get pregnant

Mycophenolate Products

- Mycophenolate mofetil (MMF)
  - Brand name: Cellcept®
- Mycophenolate sodium (EC-MPS)
  - Brand name: Myfortic®
- Mechanism of action: Depletes guanosine halting progression of activated T and B lymphocytes during S phase

MPA Metabolism



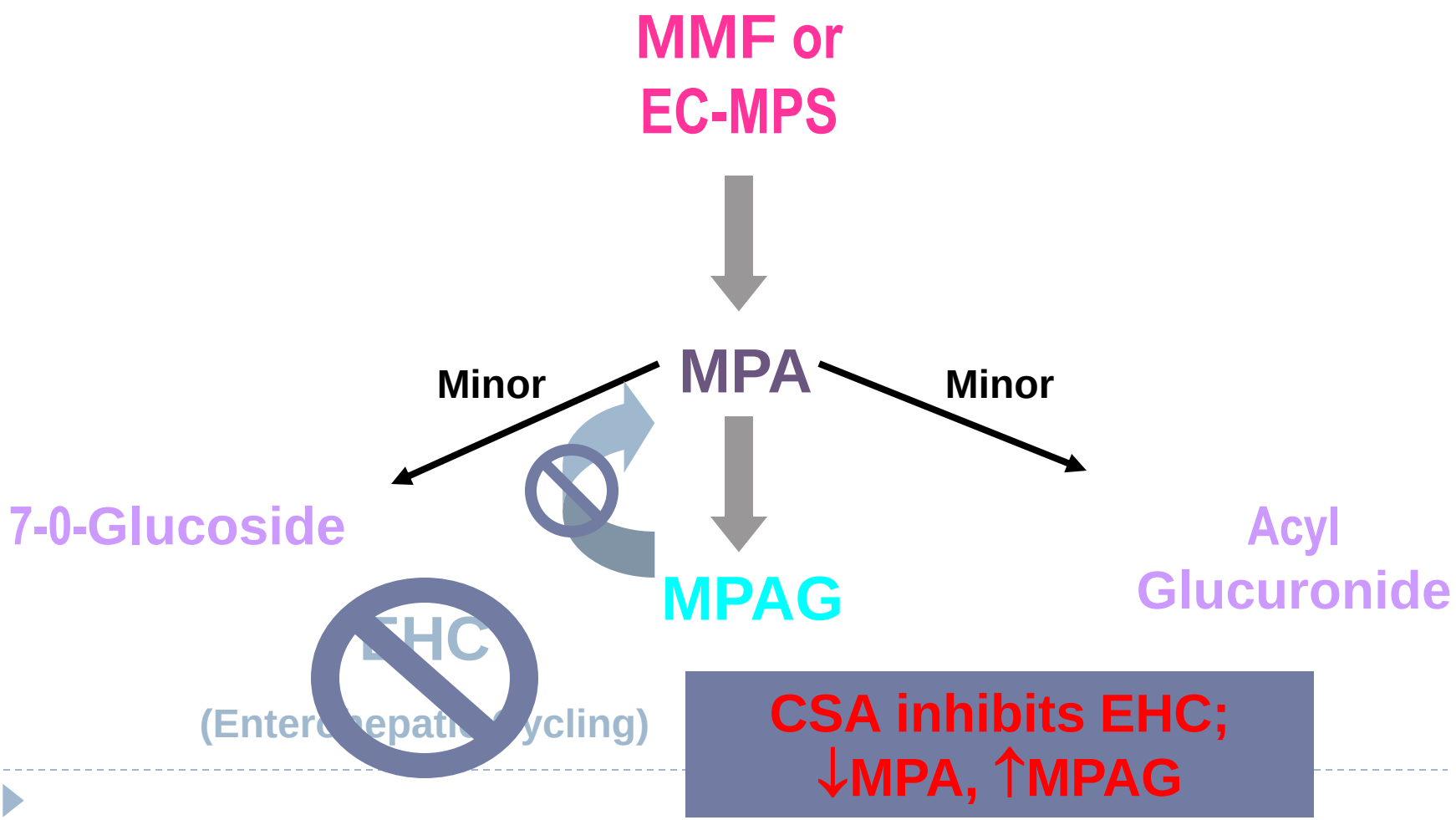
Mycophenolate Mofetil (Cellcept®)

- Usual dose: 1000 mg PO twice daily
- Adverse effects: GI problems (diarrhea, nausea, vomiting, abdominal pain), leukopenia
- Drug interactions
  - Divalent/trivalent cations (Ca, Mg, Iron)
  - CSA (decreased AUC)
  - Bile acid sequestrants (decreased AUC)
- Routes of administration
  - PO: capsules (250 mg), tablets (500 mg), suspension
  - IV: Note that PO:IV conversion is 1:1

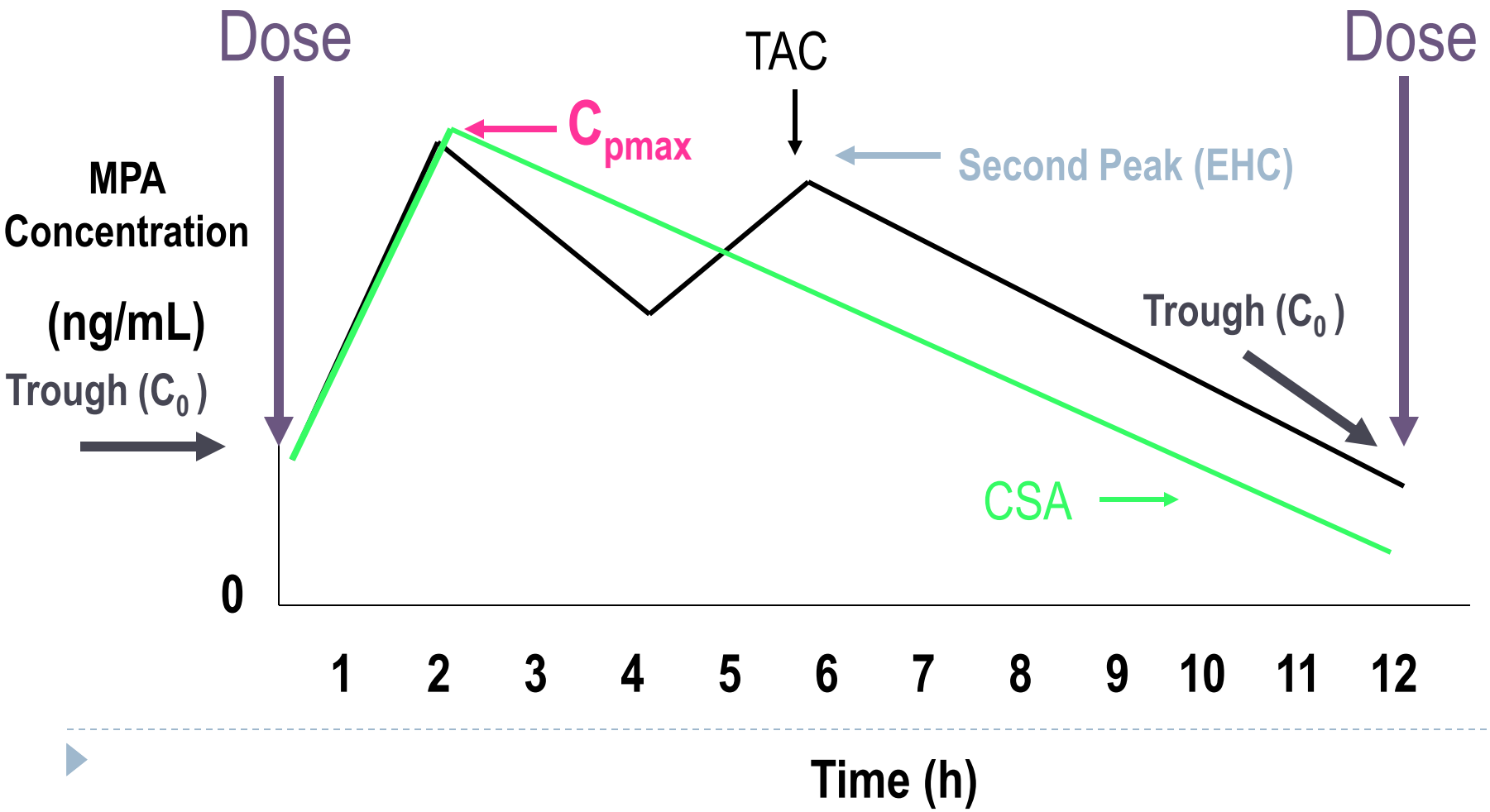
Mycophenolate Sodium (Myfortic®)

- Enteric-coated formulation
  - Proposed benefit is reduced incidence of GI toxicity
- Usual dose: 720 mg PO BID
  - Available as 180 and 360 mg tablets
- Conversions between products
  - MMF:EC-MPS
    - Eg. Cellcept® 1000 mg PO BID=Myfortic® 720 mg PO BID

CSA/MPA Drug Interaction



Effect of EHC/CSA on MPA



Mycophenolate Products: TDM

- Controversial-dose adjustments typically related to patient's ability to tolerate medications
  - 12-hour trough levels
    - May relate to toxicity and adherence
  - Mini-AUC
    - May relate to efficacy
    - If on tacrolimus:
      - MPA trough level, 30 minutes, and 2 hours post-dose
    - If cyclosporine:
      - MPA trough level, 2 hours, 3 hours, and 4 hours post-dose
    - Cannot be performed accurately if patient on mycophenolate sodium due to delayed drug release

Mycophenolate REMS

- Education for women of child-bearing potential and their providers
- Encourages appropriate forms of birth control
- Reporting pregnancies that occur to national registry

Azathioprine (Imuran®)

- Mechanism of action: Inhibits inosinic acid monophosphate dehydrogenase (IMPDH) and therefore DNA replication in rapidly dividing cells

- Usual dose
  - 1-2 mg/kg/day common maintenance dose

- Adverse effects: myelosuppression, hepatitis, cholestasis, pancreatitis

Azathioprine (Imuran®)

- Drug interactions: xanthine oxidase inhibitors, warfarin (decreases its anticoagulant effect)

- Routes of administration:
  - PO: tablets (50 mg)
  - IV: currently on drug shortage

- TDM
  - No routine drug level monitoring, consider checking 6-thioguanine levels if concerns about toxicity

Azathioprine-Xanthine Oxidase Inhibitors

- Avoid concomitant use with allopurinol and febuxostat
  - Xanthine oxidase is responsible for metabolism of azathioprine->inhibition of this enzyme->increased exposure to 6-MP->hematologic toxicity
  - Consider switch to alternative antiproliferative agent if xanthine oxidase inhibitor absolutely necessary

Leflunomide (Arava®)

- May be selected as a replacement antiproliferative in patients with concomitant viral infections (eg. BK, CMV)
- Typical dose: 40 mg PO daily (our practice is to avoid load due to tolerability issues), does have extremely long half-life
- Adverse effects: rash, hepatoxicity, neuropathy
- Teratogenic

Corticosteroids

- Prednisone (PO) or methylprednisolone (IV)
- Mechanisms of action: Prevent the expression of genes encoding cytokines, inhibit production of IL-2
- Usual dose and/or use varies by transplant center protocol
  - Steroid avoidance, rapid taper, and minimization protocols may be utilized

Corticosteroids

- Steroids (if used) are generally tapered over a period of weeks, most patients ultimately end up on ~5 mg/day

- Oral to IV conversion
  - Prednisone: Methylprednisolone ratio of 5:4
    - Prednisone 20 mg PO daily → Methylprednisolone 16 mg IV daily

Sirolimus (Rapamune®)

- Mechanism of action: Inhibits mammalian target of rapamycin (mTOR) – blocking intracellular signals past IL-2 receptor

- Initially studied for use with CSA in kidney transplant
  - Now often utilized in place of a CNI or antiproliferative

Sirolimus (Rapamune®)

- Usual dose
  - 1-5 mg PO daily
  - Avoid “loading” doses due to tolerability

- Drug interactions
  - CYP3A4
  - Administer at least 4 hours after CSA if used together

Sirolimus (Rapamune®)

- Adverse effects:
  - **Hyperlipidemia**
  - Leukopenia
  - Thrombocytopenia
  - Edema
  - Proteinuria
  - **Interstitial pneumonitis**
  - Mouth ulcers
  - **Delayed wound healing**

Sirolimus (Rapamune®)

- Role in transplant
  - Infrequently used immediately post-transplant due to wound healing complications
  - “Renal sparing” protocols
  - Beneficial in patients with malignancies (specifically skin cancers)

Everolimus (Zortress®)

- Initial dose: 0.75 mg PO twice daily
- Adverse effects: similar to sirolimus
- Drug interactions: similar to sirolimus, exception- does not need to be separated by 4 hours from CSA

mTOR Inhibitors: TDM

- Sirolimus
  - 24 hour trough
  - Goal range varies, typically 4-7 ng/mL
  - Note long half life (57-63 hours)->takes significant time to reach steady state

- Everolimus
  - 12 hour trough
  - Goal range=3-8 ng/mL
  - Half-life=30 hours

Belatacept (Nulojix®)

- Mechanism of action: selective T cell co-stimulation blocker
- First **IV-only** agent for maintenance immunosuppression
- Approved for use in kidney transplant in combination with mycophenolate, corticosteroids, and basiliximab induction

Belatacept (Nulojix®)

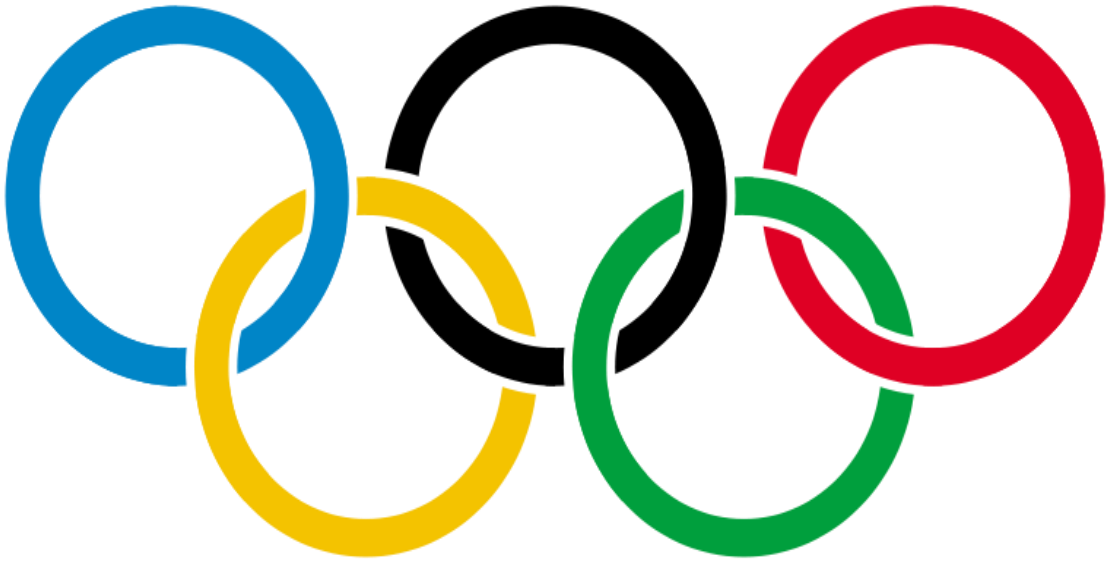
- Dose: fixed dose based on weight
  - **Initial immunosuppression:** 10 mg/kg IV on POD 0, POD 4, end of week 2, week 4, week 8, and week 12, 5 mg/kg IV end of week 16, and monthly thereafter
  - **Conversion:** 5 mg/kg IV every 2 weeks for 5 doses, then every 4 weeks thereafter
- Administration: IVPB over 30 minutes, can be given peripherally
- Common adverse effects: anemia, diarrhea, UTI, peripheral edema

Belatacept: Black Box Warnings

- Post-transplant lymphoproliferative disorder (PTLD)
  - Use limited to **Epstein-Barr virus (EBV) positive** recipients only
- Progressive multifocal leukoencephalopathy (PML)
- Requires registration for drug access via Nulojix Distribution Program

Belatacept (Nulojix®)

- Potential role in transplant
  - Not nephrotoxic
  - Decreased cardiovascular and metabolic side effects compared to CNIs
  - IV-only administration allows for direct assessment of compliance
  - Doesn’t require drug level monitoring
  - No known drug interactions



TRANSPLANT PHARMACY CLINICAL PEARLS

Pharmacokinetic Drug Interactions-Management

- For the majority of medications, CNI/mTOR inhibitor doses are not empirically reduced, rather tend to follow drug levels and adjust as necessary
  - Depends on patient's clinical status and history
- If an interacting medication is started or stopped, recommend checking trough levels
- When in doubt, look it up or consult a transplant pharmacist!

Pharmacokinetic Drug Interactions

- CYP 450 enzyme INDUCERS
- Increase drug metabolism, potentially resulting in decreased efficacy
- Examples:
  - Anti-epileptics (eg. phenytoin, carbamazepine)
  - Antibiotics (eg. rifampin)
  - Antiretrovirals (eg. efavirenz)
  - Herbals (eg. St. John’s wort)

Pharmacokinetic Drug Interactions

- CYP 450 enzyme INHIBITORS

- Decrease drug metabolism, potentially resulting in toxicity

- Examples:
  - Antifungals: azoles
  - Antibiotics: macrolides
  - Antiretrovirals: protease inhibitors
  - Hepatitis C medications: telaprevir, boceprevir
  - Cardiac meds: eg. verapamil, diltiazem, amiodarone

Pharmacodynamic Drug Interactions

- ACE inhibitors/ARBs
- NSAIDs
- Nephrotoxic drugs (additive toxicity)
- Myelosuppressive drugs (additive toxicity)

FAQ:

AM meds “held for dialysis”

Pearl:
Dialysis and Immunosuppressants

- Induction:
  - OK to hold if needed
  - Not removed by dialysis, but ideal to avoid problem of differentiating Thymo infusion-related reaction from dialysis tolerance
- Maintenance:
  - Do NOT hold tacrolimus, cyclosporine, mycophenolate, everolimus, sirolimus, steroids
  - DO hold azathioprine until after HD
  - DO hold meds for infectious ppx until after HD

FAQ:

Can I give Thymoglobulin through a peripheral line?

Pearl:
Peripheral Thymoglobulin

- Doses prepared for central administration (eg. 0.5 mg/mL concentration) CANNOT be given through a peripheral line
- For peripheral administration, doses must be:
  1. Diluted to a max of 0.25 mg/ml (not 0.5 mg/mL) AND
  2. Infused over at least 12 hours (not 6 hours)
- Phlebitis and thrombophlebitis are concerns!
  If this occurs, stop the infusion and contact the transplant pharmacist to arrange a bag with heparin and hydrocortisone mixed in.

FAQ:

My patient can’t swallow. Can I crush or dissolve his meds? Change to IV?

	PO	NG	SL	IV
Tacrolimus	✔	✔ Must use liquid	✔ Use capsules PO:SL 1:0.5-1	✔ Possible but NG preferred PO:IV 5:1
Tacrolimus, extended release	✔ Envarsus XR on formulary, Astagraf XL removed from formulary	No; consider tacrolimus	No; consider tacrolimus	No; consider tacrolimus
Cyclosporine, modified	✔	✔ Must use liquid	No	No; use cyclosporine, nonmodified
Cyclosporine, nonmodified	Nonformulary; use patient's own or cyclosporine modified	Nonformulary; use patient's own or cyclosporine modified Must use liquid	No	✔ Possible but NG preferred PO:IV 3:1
Mycophenolate mofetil (MMF)	✔	✔ Must use liquid	No	✔ PO:IV 1:1
Mycophenolic acid (MPA)	✔	No; change to MMF MPA:MMF 720:1000	No	No; change to MMF MPA:MMF 720:1000
Azathioprine (AZA)	✔	✔ Crush tablets	No	IV affected by shortage; consider MMF
Sirolimus	✔	✔ Must use liquid	No	No
Everolimus	✔	No	No	No
Prednisone	✔	✔ Crush tablets	No	use methylpred pred:methylpred 5:4

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