Managing Drug Interactions in Transplant Recipients

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Goals and Objectives

• Goal:
  – Provide the clinician with a practical overview of how to manage drug interactions in transplant recipients

• Objectives:
  – Review pharmaco-kinetic/-dynamic principles
  – Discuss factors that can affect drug levels/effects
    • Drug-drug interactions
    • Drug-nutrient interactions
  – Review management strategies
  – Cases
Immunosuppressive Drugs

Key Concepts

• Play a key role in long-term graft and patient survival
• Narrow therapeutic index drugs
  – Low levels $\Rightarrow$ rejection
  – High levels $\Rightarrow$ toxicity
• Many factors affect drug levels
  – Absorption / metabolism
  – Drug-interactions
  – Disease state
• Variability is a risk factor for rejection
Drug Interactions Contribute to Preventable ADRs

- Drug interactions represent 3-5% of preventable adverse drug reactions (in hospital)
- Important contributor to the number of ED visits and hospital admissions

Leape LL. *JAMA* 1995;274:35-43.
Typical Drug-drug Interactions
Transplant Recipient

- Tacrolimus
- Mycophenolate
- Prednisone
- Antithymocyte globulin
- Valganciclovir
- TMP/SMX
- Fluconazole
- Omeprazole
- Aspirin
- Amlodipine
- Metoprolol
- Mag Oxide
- Calcium Carb.
- Vitamin D
- Simvastatin
Drug Interactions Overview

• Pharmacokinetic ("ADME")
  – Absorption
  – Distribution
  – Metabolism
  – Excretion

• Pharmacodynamic
  – Antagonism / synergy
  – Additive efficacy or toxicity

• Pharmaceutical
  – Chemical / physical incompatibility
Pharmacokinetics 101

• **Pharmacokinetics**
  - What the body does *to the drug*
    • Absorption (from GI tract)
      - Bile
      - First pass effect (Cytochrome P450, P-glycoprotein)
    • Distribution
      - Protein binding, intracellular distribution
    • Metabolism
      - Cytochrome P-450
    • Excretion
      - Biliary excretion, enterohepatic recirculation
Pharmacokinetics
Absorption / Distribution

• Many barriers to absorption of drugs
  – CSA requires bile for absorption
  – Undergoes first-pass metabolism in GI tract (CYP3A4 and P-glycoprotein)
  – Other drugs impair absorption
    • Antacids, sevelamer (mycophenolate)
    • Posaconazole/itraconazole require acidic environment (no PPIs)
  – Food may alter absorption
    • Fresh pineapple & papaya contain papain (cyclosporine)

• Drug is distributed throughout body
  – Bound to protein / blood cells
P-glycoprotein (P-gp)

- **Transmembrane transporter**
  - *Out* of the cells and *into* the lumen of the gut
  - *Out* of the brain
  - *Into* bile
- **Located in the intestines, liver, brain, kidney**
- **ATP-dependent drug efflux pump**
  - Immunosuppressive drugs (cyclosporine, tacrolimus)
  - Chemotherapeutic agents (etoposide, doxorubicin)
  - Antiviral drugs (protease inhibitors)
- **Inhibition of P-gp** ➔ Increase drug levels
Pharmacokinetics
Metabolism

• Drug metabolism converts lipophilic compounds to polar products for excretion

• Cytochrome (CYP) P450 is a group of enzymes that catalyze oxidation of organic substances
  – Steroid metabolism
  – Metabolism of toxins/xenobiotics
  – Involved with biotransformation of many drugs
    • Cyclosporine / tacrolimus
    • Sirolimus / everolimus
Pharmacokinetics

Metabolism

• Variability in metabolism
  – Genetic polymorphisms of CYP3A4
  – Distribution and activity of CYP3A4
    • First pass in intestinal wall
    • Liver

• Drugs and other compounds may alter the activity of various CYP isoenzymes
  – Induce enzyme ➔ Increase metabolism ➔ Decrease levels
  – Inhibit enzyme ➔ Decrease metabolism ➔ Increase levels
Cytochrome P450 Isoenzymes Metabolize Many Clinically Used Drugs

<table>
<thead>
<tr>
<th>CYP1A2</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP2E1</th>
<th>CYP3A4</th>
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<tr>
<td>Acetaminophen</td>
<td>Diclofenac</td>
<td>Diazepam</td>
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<td>Mephenytin</td>
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<td>Nortriptyline</td>
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<td>Itraconazole</td>
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<td>Nifedipine</td>
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<td>Protease Inhib.</td>
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<td>Sirolimus</td>
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<td>Tacrolimus</td>
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<td></td>
<td>Terbinafine</td>
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<td>Verapamil</td>
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<td>Warfarin</td>
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## CYP3A4 Inhibitors

<table>
<thead>
<tr>
<th>Class</th>
<th>Inhibiting Drugs</th>
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<tbody>
<tr>
<td>Antibacterials (macrolide)</td>
<td>Clarithromycin, erythromycin</td>
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<tr>
<td>Antidepressant</td>
<td>Fluvoxamine, nefazodone</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Fluconazole, itraconazole, Posaconazole, voriconazole</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem, verapamil</td>
</tr>
<tr>
<td>Foods</td>
<td>Grapefruit/grapefruit juice, Pomegranate/pomegranate juice</td>
</tr>
<tr>
<td>Protease Inhibitors (HCV)</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/quinupristin</td>
</tr>
<tr>
<td>Lovastatin, simvastatin</td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>
## CYP3A4 Inducers

<table>
<thead>
<tr>
<th>Class</th>
<th>Inducing Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseizure medications</td>
<td>Carbamazepine, Fosphenytoin, Oxcarbazepine, Phenobarbital, Phenytoin</td>
</tr>
<tr>
<td>Antituberculosis</td>
<td>Rifabutin, Rifampin</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Others</td>
<td>Bosentan, Modafinil, St. John’s wort (<em>Hypericum perforatum</em>)</td>
</tr>
</tbody>
</table>
Drug Interactions Management Concepts

- Some drug interactions are useful
  - PI boosted HIV regimens
  - Diltiazem/ketoconazole to spare cyclosporine dose
- Some drug interactions can be managed clinically
  - Lower dose tacrolimus in patients on fluconazole
- Some drug interactions are profound and are contraindicated
  - Rifampin use in patients on protease inhibitors

Clinical Relevance of Drug Interactions

- **Therapeutic Index of Drug**
  - High
  - Low

- **Magnitude of interaction caused by perpetrator drug**
  - Small
  - Large

- **Concern Levels**
  - No Concern
  - Limited Concern
  - Caution
  - Serious Concern
CYP3A4 Drug-drug interactions
What to do?

• Review medications for potential interactions
• Avoid if possible
• Consider alternatives
  – Echinocandin instead of azole antifungal agent
  – Beta-blocker instead of diltiazem/verapamil
  – Quinolone (e.g. levofloxacin) instead of macrolide
  – Levetiracetam instead of phenytoin
  – Rifabutin << rifampin
  – Pravastatin/fluvastatin instead of simvastatin/lovastatin
CYP3A4 Drug-drug interactions
What to do?

• Anticipate dose change
  ➣ 50% of cyclosporine dose with voriconazole
  ➣ 33% of tacrolimus dose with voriconazole
  ➣ 25% of sirolimus dose with voriconazole
  ➣ 3x dose of cyclosporine with rifampin
  ➣ 33% more cyclosporine with efavirenz

• Monitor

Krame MR. Clin Transplant 2011;25:E163-7
Vfend prescribing information Rev 11/2011
Mathis AS. Transplant Proc 2004;36:2708-9
Immunosuppression Dosing Modifications in HIV-Infected Recipients

- **Nevirapine:**
  Same dose requirements as non-HIV infected recipients

- **Efavirenz:**
  Trough levels about 30% lower
  Increased CSA dose
  (189±44 to 275±129mg BID)

- **Protease Inhibitors:**
  4-5x ↓ CSA dose &
  50% ↑ in dosing interval
  TAC doses 80% ↓ to 0.7±0.5mg
  Dosing intervals ↑ 7x to
  80±54h

Using Drug-drug Interactions To Your Advantage

- Addition of a CYP-3A4 inhibitor for “dose sparing”
  - Diltiazem 120mg/d: ↓ CSA dose by 60%
    ↓ CSA cost by 53%
  - Ketoconazole 200mg/d ↓ CSA does by 30%
    ↓ CSA cost by 14%

- Addition of a CYP-3A4 inhibitor to decrease calcineurin inhibitor dose in patients on rifampin

Pharmacodynamics 101

• Pharmacodynamics
  – What the drug does to the body
    • Therapeutic
      – Immunosuppression to prevent allograft rejection
    • Toxic
      – Opportunistic infection (all immunosuppressive drugs)
      – Malignancies (all immunosuppressive drugs)
      – Renal dysfunction (calcineurin inhibitors)
      – Bone marrow suppression (antiproliferative agents)
Pharmacodynamic interactions

- **Immunosuppression**
  - Over immunosuppression (chemotherapy)
  - Immunostimulation (interferon alfa, echinacea)
  - Altered response to vaccines

- **Toxic effect**
  - Renal dysfunction
    - Calcineurin inhibitors and NSAIDS, aminoglycosides
  - Bone marrow suppression
    - Mycophenolate and valganciclovir
# Pharmacodynamic interactions

<table>
<thead>
<tr>
<th>Transplant medication(s)</th>
<th>Drug(s)</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine/tacrolimus</td>
<td>NSAIDs, aminoglycosides</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Valganciclovir</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Sirolimus/everolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
<td>Mycophenolate</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Sirolimus/everolimus</td>
<td>Cyclosporine</td>
<td>Hyperlipidemia</td>
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<tr>
<td>Immunosuppressive drugs</td>
<td>Chemotherapy</td>
<td>Immunosuppression</td>
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<tr>
<td>Immunosuppressive drugs</td>
<td>Vaccines</td>
<td>Reduced efficacy</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td>Live vaccines</td>
<td>Disseminated viral disease</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Fluoroquinolones</td>
<td>Tendinitis/tendon rupture</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td>Interferon/peginterferon</td>
<td>Rejection</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td>Echinacea</td>
<td>Rejection</td>
</tr>
</tbody>
</table>
Drug-Nutrient Interactions

• The “Classics”
  – Enteral nutrition / dairy products inhibits ciprofloxacin absorption
  – Isoniazid impairs vitamin B6 status
  – Ferrous sulfate impairs tetracycline absorption
  – Grapefruit juice increases simvastatin toxicity
  – Green leafy vegetables alters warfarin efficacy
  – Phenytoin decreases folic acid levels
Drug-Nutrient Interactions

- Oral drug administration with a meal* can alter rate/extent of drug absorption
  - Decreased rate of tacrolimus absorption
  - Increased bioavailability of boceprevir/telaprevir, posaconazole, valganciclovir (desired)
- Inhibit CYP3A4 activity
  - Grapefruit / grapefruit juice
  - Pomegranate / pomegranate juice

*FDA Test meal = 800-1000 Kcal (50% calories as fat (e.g. 2 fried eggs in butter, two strips of bacon, two slices of toast, 4oz hash brown potatoes, & 8oz milk)

Drug-Nutrient Interactions

Pearls of Wisdom

• Be consistent
  – What and when

• AVOID these foods:
  – Grapefruits / grapefruit juice
  – Pomegranates / pomegranate juice

• Take with food:
  – Prednisone
  – Posaconazole
  – Boceprevir / telaprevir
  – Valganciclovir
Pharmaceutical Interactions

• **Chemical / physical incompatibility**
  – Bile acid binding agents (e.g. cholestyramine)
  – Phosphate binders (e.g. sevelamer)
  – $\text{Ca}^{2+}/\text{Mg}^{2+}/\text{Al}^{3+}/\text{PO}_4^{2-}$ containing drugs
    • Quinolone antibiotics (e.g. ciprofloxacin, levofloxacin)
    • Tetracyclines (e.g. doxycycline)

• **Take only with water (empty stomach)**
  – Bisphosphonates (e.g. alendronate)
  – Levothyroxine
Pharmaceutical Interactions
It’s all in the timing

- Avoid (if possible)
- Space apart (1h before or 2h after)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Early AM</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>Bedtime</th>
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<tbody>
<tr>
<td>Cyclosporine modified</td>
<td></td>
<td>X</td>
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<td></td>
<td></td>
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<tr>
<td>Mycophenolate</td>
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<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Sirolimus</td>
<td></td>
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<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Prednisone</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Valganciclovir</td>
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<td>x</td>
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<tr>
<td>Fluconazole</td>
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<tr>
<td>Alendronate</td>
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<td>x</td>
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HIV and the Transplant Recipient

• Managing transplant recipients with HIV is challenging:
  – Antiretroviral medications can induce or inhibit CYP3A4 and P-glycoprotein
  – Concomitant medications may interfere with absorption of antiretroviral medications
  – Adverse effects (e.g. bone marrow suppression) may be additive

• Transplant care provider ↔ HIV care provider
HIV and the Transplant Recipient
Multiple drug-drug interactions

• Atazanavir (PI) inhibits CYP3A4
  – Increase cyclosporine/tacrolimus/sirolimus/everolimus
• PPIs are commonly used in transplant recipients
  – Atazanavir best absorbed in low pH (acidic environment)
  – PPIs decrease atazanavir absorption
    • Avoid PPI use
  – No interaction with PPIs when ritonavir-boosted atazanavir is used
HIV and the Transplant Recipient Effect on Immunosuppressive Drugs

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Sirolimus</th>
<th>Tacrolimus</th>
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<tbody>
<tr>
<td>No ARVs</td>
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<tr>
<td>Dose (mg)</td>
<td>334±122</td>
<td>8.2±4.2</td>
<td>7-9</td>
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<tr>
<td>Interval (h)</td>
<td>12</td>
<td>24</td>
<td>12</td>
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<tr>
<td>Trough (ng/mL)</td>
<td>251±116</td>
<td>23.3±5</td>
<td>3-30</td>
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<td>NNRTI</td>
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<tr>
<td>Dose (mg)</td>
<td>215±95</td>
<td>ND</td>
<td>3.1±1.4</td>
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<tr>
<td>Interval (h)</td>
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<td>ND</td>
<td>12</td>
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<tr>
<td>Trough (ng/mL)</td>
<td>113±57</td>
<td>ND</td>
<td>6.4±2.9</td>
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<td>Protease Inhibitor</td>
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<tr>
<td>Dose (mg)</td>
<td>51±43</td>
<td>1±0</td>
<td>0.7±0.5</td>
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<tr>
<td>Interval (h)</td>
<td>19±11</td>
<td>92±72</td>
<td>80±84</td>
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<tr>
<td>Trough (ng/mL)</td>
<td>176±167</td>
<td>10.3±9/3</td>
<td>6.6±6.6</td>
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Hepatitis C in Transplant Recipients

- Large unmet need for treatment after liver transplantation
- Boceprevir and Telaprevir inhibit serine NS3/4A protease
  - Potent inhibitors of CYP3A4
- Triple Regimen is the standard of care
  - Peginterferon alfa
  - Ribavirin
  - Protease inhibitor (boceprevir, telaprevir)
HCV Protease Inhibitors
Potent Inhibitors of CYP3A4

- Boceprevir & telaprevir inhibit metabolism of cyclosporine and tacrolimus
- Cyclosporine and tacrolimus do not affect the PK of boceprevir and telaprevir

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<thead>
<tr>
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<tr>
<td>CSA</td>
<td>1800</td>
<td>11.2</td>
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<td>CSA + Boceprevir</td>
<td>4840</td>
<td>15.5</td>
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<tr>
<td>Tac</td>
<td>21.8</td>
<td>36.7</td>
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<tr>
<td>Tac + Boceprevir</td>
<td>345</td>
<td>61.3</td>
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<tr>
<td>CSA</td>
<td>18.8</td>
<td>12</td>
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<tr>
<td>CSA + Telaprevir</td>
<td>85.3</td>
<td>42.1</td>
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<tr>
<td>Tac</td>
<td>33.6</td>
<td>40.7</td>
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<tr>
<td>Tac + Telaprevir</td>
<td>2620</td>
<td>196</td>
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HCV in Liver Transplant Recipients
Treatment Considerations

• **Treatment duration:** Boceprevir (44 wks)
  Telaprevir (12 wks)

• **Effect on drug levels** CSA << Tac

• **Dosing:**
  - Cyclosporine Daily
  - Tacrolimus Once a week
  - Sirolimus Once a week

• **Treatment associated with significant anemia**
**HCV and HIV Protease Inhibitors**

- FDA issues warning on use with boosted HIV regimens
- Efavirenz decreases PI levels
- Decreased drug levels may reduce efficacy

### Boceprevir decreases PI trough levels:

<table>
<thead>
<tr>
<th></th>
<th>Ritonavir + Atazanavir</th>
<th>Ritonavir + Lopinavir</th>
<th>Ritonavir + Darunavir</th>
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<tbody>
<tr>
<td>Trough level</td>
<td>↓49%</td>
<td>↓43%</td>
<td>↓59%</td>
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### PI regimens decrease boceprevir AUC:

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<th>Ritonavir + Lopinavir</th>
<th>Ritonavir + Darunavir</th>
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<tbody>
<tr>
<td>Boceprevir (AUC)</td>
<td>No change</td>
<td>↓45%</td>
<td>↓32%</td>
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</table>

Case 1
Drug-drug Interaction

65 year old male s/p liver transplant 1 year ago for HBV cirrhosis. He calls clinic complaining of headaches and nausea. He started treatment of *H. pylori* infection one week ago.

**Labs:**
- Scr = 2.7 (normally 1.2)
- K = 5.5
- WBC = 6.7
- Tacrolimus = 19.7

**Current meds:**
- Tacrolimus 4mg PO BID
- Mycophenolate 1000mg PO BID
- Prednisone 5mg PO daily
- Entecavir 0.5mg PO daily
- Metoprolol 50mg PO BID
- Prevpac: Amoxicillin 1gm PO BID
  - Lansoprazole 30mg PO BID
  - Clarithromycin 500mg PO BID
Case 2

Drug-drug Interactions

53 year old male s/p OLT for Non-alcoholic steatohepatitis. He has a h/o of a *C. glabrata* endovascular infection. Plan is to transition to posaconazole to complete a course of antifungal therapy.

Allergies: Penicillin, Voriconazole -> increased LFTs

**Current meds:**

- Tacrolimus 2mg PO BID
- Mycophenolate 1000mg PO BID
- Prednisone 20mg PO daily (taper)
- Valganciclovir 900mg PO daily
- Caspofungin 50mg IV daily
- Lansoprazole 30mg PO daily

**To do:**
Case 2

Drug-drug Interactions

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- Caspofungin 50mg IV daily
- Lansoprazole 30mg PO daily

**To do:**
- ➔ Tacrolimus 1mg PO BID
- ➔ Posaconazole 400mg PO BID (with meal)
- ➔ Famotidine 40mg PO daily

Monitor Tacrolimus level
Posaconazole level
Case 3
Antiretrovirals in Transplantation

55 year old HIV+ male s/p kidney transplant for hypertensive nephropathy.

**Current medications:**
- Cyclosporine modified 300mg PO BID
- Mycophenolate 1000mg PO BID
- Prednisone 20mg PO daily (taper)
- Fluconazole 100mg PO QMondays
- TMP/SMX DS 1 tab PO daily
- Valganciclovir 450mg PO daily
- Amlodipine 10mg PO daily
- Lansoprazole 30mg PO BID
- Aspirin 325mg PO daily
- Metoprolol 100mg PO BID

**Labs:**
- Scr = 2.1 (2.8 yesterday)
- K = 4.8
- WBC = 5.7
- Plts = 135K
- Cyclosporine = 221 ng/mL

**Antiretroviral regimen (at home):**
- Kaletra (ritonavir/lopinavir)
- Truvada (tenofovir/emtricitabine)
Case 3
Antiretrovirals in Transplantation

55 year old HIV+ male s/p kidney transplant for hypertensive nephropathy.

**Current medications:**
- Cyclosporine modified 300mg PO BID
- Mycophenolate 1000mg PO BID
- Prednisone 20mg PO daily (taper)
- Fluconazole 100mg PO QMondays
- TMP/SMX DS 1 tab PO daily
- Valganciclovir 450mg PO daily
- Amlodipine 10mg PO daily
- Lansoprazole 30mg PO BID
- Aspirin 325mg PO daily
- Metoprolol 100mg PO BID

**To do:**
- Cyclosporine modified 25mg PO daily

**Start:**
- Kaletra (ritonavir/lopinavir) 1 tab PO BID
- Truvada 1 tab PO every other day

- Amlodipine 5mg PO daily
Drug-drug Interactions

Between Immunosuppressives

- Cyclosporine \(\uparrow\) Sirolimus exposure
  - Give sirolimus 4 hours after cyclosporine
- Cyclosporine \(\uparrow\) Everolimus exposure
- Cyclosporine \(\downarrow\) Mycophenolic acid exposure
- Tacrolimus \(\uparrow\) Mycophenolic acid exposure
- Everolimus \(\Rightarrow\) Tacrolimus bioavailability

- What to do? Be consistent!

What to discuss with patients

- Always read labels carefully
- Ask doctor/pharmacist/nurse what they need to avoid when prescribed a new medication
- Check before taking any OTC medications
- Use ONE pharmacy for all their medication needs
- Keep a record of all medications, OTC drugs and dietary supplements
- Keep all healthcare providers informed about all of the medicines they take
Five Simple Things to Remember

- **Current** medication list
- **Check** for interactions
- **Consistency**
- **Avoid** interactions (if possible)
- **Empower** the patient
Drug Interaction Resources

- Micromedex® 2.0 (online & mobile)
- Lexicomp™ (mobile & online)
- Facts & Comparisons® (online & mobile)
- Epocrates® (mobile & online)
- Medscape® (online & mobile)
- Package insert / manufacturer
- PubMed®/Medline® literature search
- Ask your pharmacist