Infection in the Solid Organ Transplant Patient
adapted from Osler chapter by David Lim, M.D., Ph.D. and Aruna Subramanian, M.D.

50-75% of pts get infected w/in 1st year

INTERCONNECTED GOALS
1. prevent & treat rejection
2. prevent & treat infxn

For the toxic patient...
1. broadly cover for GP, GN, anaerobes
2. consider covering fungus, MRSA, VRE, CMV

Outcomes depend on...
1. the direct effect of infxn
2. indirect effects of infxn: decrease in immunosuppression -> worsens acute & chronic allograft injury -> potential for malignancy

ANTILYMPHOCYTIC ANTIBODIES
- for induction tx immediately post-tx, and for steroid-resistant acute rejection
- polyclonal preparations: antithymocyte globulin, antilymphocyte serum
- monoclonal preparations: OKT3 (murine Ab to CD3 T-cell receptor), daclizumab, basiliximab
- infxn risks: herpes viruses (esp CMV), fungus, mycobacteria
- s/e: neutropenia, thrombocytopenia, hemolysis, allergic rxns, fevers, chills, hypotsn, malaise
IMMUNOSUPPRESANTS

Corticosteroids
- inhibit cytokine prod, leukocyte fxn, arachidonic acid metab, plt activ factor, vasc permeability; net effect is inhibition of T-cell activation & prolif
- inflx risks: bacteria, mycobacteria, PCP, herpes, hep B & C, fungus, Strongyloides stercoralis; SiSx (incl x-ray findings) greatly diminished until late into inflxn, even though microbial burden higher than in normal hosts

Azathioprine (Imuran)
- inhibits purine synthesis & salvage; greatest effect is on actively dividing lymphs
- inflx risk: herpes, papillomaviruses, fungi, mycobacteria, S. stercoralis, other intracellular orgs
- s/e: marrow suppression, neutropenia

Mycophenolate Mofetil (MMF) (Cellcept)
- mycophenolic acid prodrug; selective, reversible inhibition of guanosine synthesis -> inhibits B & T lymph prolif
- often replaces Aza b/c more potent anti-rejection agent & added effect not assoc w/ major incr of inflxn or lymphoma
- inflx risk: same as Aza
- s/e: less neutropenia, cramps, diarrhea

Calcineurin Inhibitors (CI): Cyclosporine (CYA) and Tacrolimus (FK506, Prograf)
- prevent T-cell activation & proliferation
- Tacrolimus is 10-100x more potent than CYA
- inflx risk: replicating herpes group viruses, incl CMV & EBV
- s/e: htn (CYA>tac), hyperchol, nephrotoxicity, DM (tac>CYA)
- drug-drug interactions:
  > incr p450 metabolism: rifampin, INH, nafcillin
  > decr p450 metabolism: macrolides (eryth>clarith>azithro), azoles (keto>itra/vori>fluc)
  > enhance nephrotoxicity (see no chg in CI conc): high dose fluoroquinolones, bactrim, ampho, aminoglycosides

Rapamycin (Sirolimus)
- inhibits ribosomal protein synthesis & progression to DNA synthesis -> prolongs cell cycle G1 to S phase progression
- less potent then calcineurin inhibitors, but inhibits B-cell Ig synthesis, Ab-dependent cellular cytotoxicity, lymphocyte-activated killer cells & NK cells
- can be used w/ CYA
- inflx risk: PCP
- s/e: aphthous ulcers, hyperchol, htn, marrow suppression, & can potentiate CYA nephrotox
POST-TRANSPLANT INFECTION TIMELINE

<4 weeks
- from donor or recipient: HBV, HCV, HIV, bacteria or fungi in lungs/sinuses of CF pts, resistant nosocomials (VRE, MRSA)
- post-surgical infections: obstructed stents, devitalized tissues, fluid collections
- nosocomial infection: aspiration pna, line sepsis, uti

2-6 months
- residual from peri-op period: hematoma, lymphocele, ischemic tissue
- opportunistic: PCP, aspergillus, listeria, nocardia, toxoplasmosis, mycobacteria, endemic mycoses
- reactivation of latent viruses: CMV, EBV, HSV, VZV, Hep B or C
- routine prophylactic antimicrobial tx -> later occurrence of many infections beyond 2-6 mo period

>6 months
- 80% patients: infection problems similar to community, ie. no opportunistic
- 10%: chronic or progressive immuno-modulating viral infections (HBV, HCV, CMV, EBV, papillomavirus, BK virus, HIV); if not treated -> tx organ destruction +/- malign (PTLD, HCC, KS)
- 10%: chronic transplant ID problems; poor allograft fxn d/t rejection requires high-dose immunosuppression so incr risk of opportunistics (e.g. crypto, PCP, nocardia, aspergillus, listeria), also incr rates of C. diff; usually need prophylactic antimicrobial tx
Exceptions to the usual sequence of infections after transplantation suggest the presence of unusual epidemiologic exposure or excessive immunosuppression. HSV denotes herpes simplex virus, CMV cytomegalovirus, EBV Epstein–Barr virus, VZV varicella–zoster virus, RSV respiratory syncytial virus, and PTLD post-transplantation lymphoproliferative disease. Zero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted lines and arrows indicate periods of continued risk at reduced levels. Adapted from Rubin et al

COMMON INFECTION

CMV
- hi prevalence & increases immunosuppression -> risk of PCP, nocardia, listeria
- Sx: fever, leukopenia, thrombocytopenia, mild hepatitis, anorexia, malaise; can preferentially infect allograft
- Dx: CMV Ag, CMV pcr, histology, Cx sterile sites (not urine or sputum); note that CMV serologies only to assess risk and not dx active viremia or infxn
- Mgmt: CMV prophylaxis for all CMV-neg recipients or cadaveric organ recipients regardless of donor/recipient CMV status (50% of therapeutic IV gangciclovir which is 5 mg/kg, or valgan 900 mg po qd or 450 mg po qd for renal tx pt); CMV surveillance q3mo post-therapy to prevent relapsing infxn; preemptive tx for pts getting anti-lymphocytic Ab induction or tx for acute rejection; tx active CMV for >=2-4wks of induction w/ IV gangc or PO valgan, then maintenance tx x 3mos; anti-CMV hyperimmune globulin can be used for severe for relapsing dz

HSV-1 and HSV-2
- usu 1st month post-tx (w/o prophylaxis)
- Sx: localized derm changes (orolabial, genital, perianal) +/or invasive infxn (esophagitis, hepatitis, pneumonitis)
- Mgmt: acyclovir IV/PO depending on severity

VZV
- usu >3 months post-tx
- primary dz assoc w/ hi mortality (so important to vaccinate pre-tx)
- Sx: dermatomal or disseminated rash; visceral dz incl pneumonitis, hepatitis, encephalitis
- Mgmt: acyclovir IV/PO depending on severity

HHV-6 and HHV-7
- can trigger CMV activation
- Sx: exanthem subitum (macular rash, then hi fever); mono-like illness + neutropenia; meningitis
- Mgmt: decr immunosuppression & add foscarinet, ganciclovir, or cidofovir

HHV-8
- Sx: Kaposi’s sarcoma, primary effusive lymphoma, Castleman’s syndrome, fever, marrow suppression
- Mgmt: decr immunosuppression & add xrt, chemotx, and/or antivirals

Others
BK virus (renal transplant)
Hepatitis B and C
Urinary Tract Infection
Fungal Infections
## TRANSPORT MEDICATION PROTOCOL

<table>
<thead>
<tr>
<th>Immunosuppressive regimen</th>
<th>Target drug levels[^1]</th>
<th>First year</th>
<th>Second Year</th>
<th>Thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Thymoglobulin induction Tacrolimus (Prograf), Mycophenolate (Cellcept), Steroids (possible d/c after 3 months)</td>
<td>Tacrolimus: 5-8 ng/ml</td>
<td></td>
<td>3-6 ng/ml</td>
<td>3-6 ng/ml</td>
</tr>
<tr>
<td><strong>B</strong> Cyclosporine (Gengraf), Mycophenolate (Cellcept), Steroids</td>
<td>250-300 ng/ml</td>
<td>175-250 ng/ml</td>
<td>100-150 ng/ml</td>
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<tr>
<td><strong>C</strong> Tacrolimus (Prograf), Sirolimus (Rapamune), Steroids</td>
<td>Tacrolimus: 3-6 ng/ml</td>
<td></td>
<td>Sirolimus: 7-12 ng/ml</td>
<td></td>
</tr>
<tr>
<td><strong>D</strong> Cyclosporine (Gengraf), Sirolimus (Rapamune), Steroids</td>
<td>Cyclosporine: 100-150 ng/ml</td>
<td></td>
<td>Sirolimus: 7-12 ng/ml</td>
<td></td>
</tr>
<tr>
<td><strong>E</strong> Sirolimus (Rapamune), Mycophenolate (Cellcept), Steroids</td>
<td>Sirolimus: 7-12 ng/ml</td>
<td></td>
<td>5-8 ng/ml</td>
<td>5-8 ng/ml</td>
</tr>
<tr>
<td><strong>F</strong> Cyclosporine or Tacrolimus, +/-Azathioprine (Imuran), Steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>G</strong> Azathioprine or Mycophenolate, Steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Guideline for Immunosuppressive Regimens**

Immunosuppressive regimens are selected by the treating transplant team. Regimen A is our currently recommended regimen for the majority of patients. Regimen C-E are more aggressive regimens usually reserved for those at high risk for rejection or who have rejected on regimen A. Regimens F and G are less immunosuppressive and are considered for patients with BK nephropathy, and for patients doing well with 0-mismatched transplants. Selection of cyclosporin vs. tacrolimus in regimen F determined by patient risks and potential toxicities. Hirsutism and hyperlipidemia more common with cyclosporin. Glucose intolerance more common with tacrolimus. Regimen G may be used for patients with good function, and toxicity or contraindications for calcineurin inhibitors.
### Guideline for Prednisone taper

Solumedrol: 250mg IV intraoperatively, then 125mg IV POD#1, 60mg IV POD#2, and 30mg IV POD#3 (administered 1 hour prior to Thymoglobulin). Decadron may be used as an alternative to Solumedrol at 50 mg IV intraoperatively, 50 mg IV POD#1, 25 mg IV POD#2, and 12.5 mg POD#3. On POD#4 start prednisone po: 30mg qd x 1 day, then decrease by 2.5-5mg every day until dose of 5mg QD is reached by day 10-14. If patients are not at high risk for Addison’s or rejection, and patients are able to tolerate 2 non-steroid immunosuppression medications (such as MMF and Tacrolimus), prednisone may be further tapered and discontinued at day 90 post-transplant.

### Guideline for Mycophenolate mofetil (Cellcept)

1000 mg BID for all patients. Decrease dose if diarrhea or leukopenia, or MPA & MPA-G (inactive metabolite) levels warrant. Levels should be a 12 hour trough and drawn just before the next scheduled dose. Monitoring is recommended 2-3 weeks after transplant and periodically thereafter to evaluate adequacy of dosing. Steady state is achieved 5 days after a dose change. Target MPA level is 1-3.5mcg/ml. Typical MPA-G level is 35-100mcg/ml by HPLC.iii[3] Trough MPA level > 4.0 mcg/ml & MPA-G level < 40mcg/ml may indicate overimmunosuppression and low phase II hepatic conjugating capability and may require a decrease in dose. Conversely, high trough MPA-G levels may indicate high hepatic conjugating capacity & may require an increase in dose to maintain goal MPA levels.

### Guideline for Tacrolimus

Tacrolimus is our preferred calcineurin inhibitor. It is started at 0.2mg/kg/d in divided doses every 12 hours after transplant has shown signs of improvement after surgery (generally when Scr < 3 mg/dl or when Scr has decreased to 50% of post-operative baseline). Dose is adjusted to achieve target levels as described in table above. AUC is increasingly used to monitor and adjust drug dosing. AUC should be done initially 2 weeks post-transplant. Clinicians must be familiar with drug toxicities and interaction with other medications.

#### Tacrolimus AUC

1. Schedule appointment in infusion clinic. Test may take up to 4.5 hours. Tacrolimus dose should be stable for at least 3 days. Patients should bring their Tacrolimus dose to the clinic & not eat before the test.
2. Tacrolimus blood levels will be drawn at 0, 1, 2 & 4 hours after the dose.iv[4]
3. C₀ must be a 12-hour trough level. Tacrolimus dose is taken immediately after C₀ drawn. Patient may eat between C₀ and C₁ sampling.
4. AUC₁₂ is estimated by formula: 10 + 1.4*C₀ + 0.8*C₁ + 1.6*C₂ + 5.5*C₄. Pharmacist can provide analysis with graph.
5. Target AUC₁₂v[5] = 100+ 33 ng x hr/ml. Adjust Tacrolimus dose as clinically indicated.

### Guideline for Cyclosporin A (Gengraf)

Cyclosporin A has been available for 2 decades and was the first calcineurin inhibitor available for clinical use. It is started at 6-8 mg/kg/d in divided doses every 12 hours after transplant has shown signs of improvement after surgery (generally when Scr < 3 mg/dl or when Scr has decreased to 50% of post-operative baseline). Dose is adjusted to achieve target levels as described in table above. AUC may be used to monitor and adjust drug dosing, but experience with Cyclosporin AUCs is less compared to Tacrolimus. Clinicians must be familiar with drug toxicities and interaction with other medications.

#### Cyclosporine AUC:

1. Schedule appointment in infusion clinic. Test may take up to 4.5 hours. Cyclosporine dose should be stable for at least 4 days. Patients should bring their Cyclosporine dose to the clinic & not eat before the test.
2. Cyclosporine blood levels will be drawn at 0, 1, 2, 3 and 4 hours after the dose.v[6]
3. C₀ must be a 12-hour trough level. Cyclosporine dose is taken immediately after C₀ drawn. Patient may eat between C₀ and C₁ sampling.
4. AUC₀₄ is estimated by the formula: 256 + C₁ + 0.9*C₂ + 1.4*C₃. Pharmacist can provide analysis with graph.
5. Target AUC₀₄ = 4400-5500 mcg x hr/L for the first 3 months after kidney transplant.vii[7] Adjust Cyclosporine dose as clinically indicated.

### Guideline for Thymoglobulin

We currently use Thymoglobulin for all cadaveric and live donor kidney transplants, unless the patient has a contraindication. 1.5mg/kg qd X5 doses, first dose intra-op. Reduce dose by ¼ if ANC is less than 1000 or if platelet count is between 50,000-75,000. Hold drug if ANC is less than 500 or if platelets <50,000.
Prophylactic Medications

<table>
<thead>
<tr>
<th>Induction antibody (thymoglobulin) given?</th>
<th>CMV Status: Donor/Recipient</th>
<th>Prophylaxis (see ‘CMV prophylaxis recommendation’ below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>Donor positive/Recipient negative</td>
<td>High risk regimen, and continue valgancyclovir until ALC &gt;500.</td>
</tr>
<tr>
<td>YES</td>
<td>Donor positive/Recipient positive</td>
<td>Intermediate risk regimen, and continue valgancyclovir until ALC &gt;500.</td>
</tr>
<tr>
<td>YES</td>
<td>Donor negative/Recipient negative</td>
<td>Low risk regimen, and continue valgancyclovir until ALC &gt;500.</td>
</tr>
<tr>
<td>NO</td>
<td>Donor positive/Recipient negative</td>
<td>High risk regimen</td>
</tr>
<tr>
<td>NO</td>
<td>Donor positive/Recipient positive</td>
<td>Low risk regimen</td>
</tr>
<tr>
<td>NO</td>
<td>Donor negative/Recipient negative</td>
<td>See ‘HSV prophylaxis recommendation’ below</td>
</tr>
</tbody>
</table>

**CMV Prophylaxis recommendation:**
- High risk regimen: Cytogam (see ‘Guideline for Cytogam’ below) + valgancyclovir 450mg PO qd X 6 months.
- Intermediate risk regimen: Valgancyclovir 450mg PO qd X 6 months.
- Low risk regimen: Valgancyclovir 450mg PO qd for 90 days.
- Dose reduce Valgancyclovir for renal insufficiency.
- Restart Valgancyclovir 450mg PO qd for 90 days if acute rejection treated with high dose steroids, OKT3, or thymoglobulin.
- Continue Valgancyclovir 450mg PO qd lifelong if patient develops CMV disease after prophylaxis.

**HSV Prophylaxis recommendation:**
- For all patients, regardless of CMV status or antibody therapy given: After CMV prophylaxis or treatment., use acyclovir 200-400mg PO BID lifelong for patients with history of H. zoster or H. simplex.

**Guideline for Cytogam (CMV-IVIG):**
Cytogam should be given for all CMV donor positive/recipient negative kidney & kidney/pancreas transplants, whether or not they received induction antibody therapy. The dosing regimen for kidney transplant consists of 150mg/kg within 72 hours of transplant, and 100mg/kg at 2, 4, 6 & 8 weeks post-transplant, then 50mg/kg at weeks 12 & 16. For kidney/pancreas transplant the regimen consists of 150mg/kg within 72 hours of transplant, and at 2, 4, 6, & 8 weeks post-transplant, then 100mg/kg at 12 & 16 weeks.

**Guideline for BK Polyoma Virus in Renal Transplantation**
BK infection recently identified as a common opportunistic infection in renal tx, often leading to BK nephropathy & loss of tx fxn. Emergence appears related to newer immunosuppressive regimens. Optimal approach to dx & mgmt unknown. Examine urine for decoy cells & cyto (PAP smear) and blood for qualitative/quantitative PCR for BK virus to help detect & monitor. Kidney bx often required to dx BK nephropathy & r/o other causes of tx dysfunction. Tx of BK nephropathy: first decr immunosuppression by decreasing doses or changing to less immunosuppressive regimens. Can add cidofovir, but optimal dosing & duration unknown.

**Guideline for Cidofovir**
Cidofovir may be used to treat BK nephropathy. Confirm dx of BK nephropathy. Clinicians must be familiar with dosing, complications, monitoring. Doses from 0.25 – 1 mg/kg/dose q 2-3 week x 2-4 doses +/- Probenecid.ξ
- Probenecid 2 grams 3 hrs prior to Cidofovir dose & 1 gm 2 & 8 hrs post Cidofovir dose is recommended. Patient must be adequately hydrated w/ >=1 L NS IV immed before Cidofovir infusion. A second NS liter may be given if tolerated.

**PCP and UTI Prophylaxis**
Septra DS 1 tablet PO 3 times a week (or Septra SS 1 tablet qd) for 6 months. For sulfa allergic patients, use inhaled pentamidine 300mg q month and Trimethoprim 100mg PO QD X 6 months.

**Antifungal Prophylaxis**
Clotrimazole 10mg Troche (Mycelex). Dissolve in mouth TID after meals, for 90 days post transplant. Alternatively, may use nystatin swish & swallow 5ml TID & hs for 90 days after transplant. For pancreas transplant only, fluconazole 100mg qd for 1 year, although consider for diabetic recipients. Watch for drug interaction with tacrolimus, cyclosporine, sirolimus if using clotrimazole or fluconazole. Check calcineurin drug level 2 weeks after discontinuation of clotrimazole or fluconazole to ensure therapeutic level.