Kidney Transplant Program

Post-Transplant Medication Tip Sheet for Nephrology Residents & Fellows

AUTHORS

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PURPOSE

This Clinical Tip Sheet is intended as a guide to assist Nephrology residents and fellows with medication orders and discharge prescriptions for kidney transplant patients admitted at St. Michael's Hospital.

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SECTION 1: NEW KIDNEY TRANSPLANT ADMISSIONS

TYPES OF KIDNEY TRANSPLANTS:

- Deceased donor
  - A kidney becomes available to a recipient on the waiting list when an organ donor passes away (DCD = donation after cardio-circulatory death, NDD/DNC = death determination by neurologic criteria)
  - Recipients can be called in for a transplant at any time of the day or night
- Living donor
  - A kidney is donated from a living individual to another
  - Individuals may be genetically related (living related), non-related (living emotional, altruistic/anonymous, paired exchange)
  - Transplants are typically scheduled on Monday, Tuesday, or Thursday mornings (~10 am)

CLINICAL IMMUNOSUPPRESSION:

- Induction
  - IL-2 receptor antagonist (basiliximab, Simulect®)
  - Anti-Thymocyte Globulin (rATG, Thymoglobulin®)
- Maintenance
  - Calcineurin inhibitor (tacrolimus > cyclosporine)
  - Antimetabolite (mycophenolate > azathioprine)
  - Steroids (methylpredniosolone, prednisone)

INDUCTION OF IMMUNOSUPPRESSION:

- Determining immunologic risk
  - High risk
    - Presence of donor specific antibodies (DSAs), these transplants are **not** performed at SMH
    - ?highly sensitized patients (HSP; cPRA ≥80%)
      - In the presence of negative flow and virtual cross-match, these patients may be considered to be either high or low risk based on interpretation by the transplant nephrologist
  - Low/standard risk
    - Absence of DSAs
    - Almost all patients at SMH are considered to be low/standard risk in context of negative flow and virtual cross-match at time of transplant
  - Steroid avoidance
    - A prednisone-free protocol may be preferred for some patients (e.g. pre-diabetes, prior intolerance), but has been associated with increased risk of rejection
- Induction of immunosuppression (SMH protocols)
  - **All patients** (including prednisone-free protocol)
    - Methylprednisolone
      - Dosing
        - 2 mg/kg IV x 1 on call to OR
        - Then, 1 mg/kg IV Q12H x 48h (total of 4 doses) starting on POD#0
      - Tips for validation
        - When validating on call methylprednisolone dose, please add max dose of 1
        - Please round all doses to nearest 5 mg
  - **High risk** induction: **rATG (Thymoglobulin®)** ***Tip: see Thymoglobulin order set in Soarian and/or Thymoglobulin Protocol in Pharmacy Documents (UnityNet → Pharmacy → St. Michael's → Document Library)**
    - T-cell depleting polyclonal antibody: anti-CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chains, and β2 micro-globulin
    - Indications
      - Prednisone-free protocol
      - Some highly sensitized patients, depending on transplant nephrologist's usual practice
    - Dosing: **Usual initial dose is 1 mg/kg or less**. Thereafter, **usual daily dose for induction is 1.5 mg/kg**, for total **cumulative dose of ~3-5 mg/kg.**
      - A smaller first dose (e.g. 50 mg) is preferred to reduce incidence of cytokine release syndrome

- Dose reassessed daily based on WBC and platelets: reduce dose by 50% if WBC 2-3 or platelets 50-75, hold if WBC <2 or platelets <50

Example regimens (70 kg)
- Target 3 mg/kg (225 mg): 50 mg, 75 mg, 100 mg
- Target 5 mg/kg (350 mg): 50 mg, 100 mg, 100 mg, 100 mg

- Always **round to nearest 25 mg vial** (~$325/vial)

▪ Can be administered with **central or peripheral line** (central line preferred for higher cumulative targets as peripherally irritating)

▪ Dilution and rate of administration

Access	Dose	Dilution	Run-in
Central	≤125 mg	250 mL NS	8 hrs
Central	>125 mg	500 mL NS	12 hrs
Peripheral	All	500 mL NS	12 hrs

▪ Start time
- First dose: upon return to 8CS
- Subsequent doses: usually ~5-6 pm (runs overnight)

▪ Pre-meds (i.e. methylprednisolone, acetaminophen, and diphenhydramine) should be ordered and administered for at least the first 2 doses
- RN may also give patient's usual dose of methylprednisolone 1 mg/kg Q12H prior to infusion if administration time coincides with administration time of Thymoglobulin

▪ Preparation
- Bags are made by Pharmacy in sterile room
- Expiry: 24 hrs
- Refrigerated (but stable at RT x 24 hrs)
- Do not tube

o **Low/standard risk** induction: **basiliximab (Simulect®)**

▪ Indications
- Almost all patients with negative flow and virtual cross-match
- Some highly sensitized patients, depending on transplant nephrologist's usual practice

▪ Dosing: 20 mg IV x 2 doses (first dose on call to OR, second dose on POD#4 at 10:00H)

▪ Validation tips
- For post-op basiliximab dose, enter date in additional SIGs

▪ Preparation
- Floor stock on 8CS, made by RN and used immediately
- If made by Pharmacy, expiry of 24 hrs (refrigerate)
- Cost: ~$1500 per dose

<u>MAINTENANCE OF IMMUNOSUPPRESSION</u>:

- CNI (tacrolimus>cyclosporine)
  - Tacrolimus
    - Formulations: **Advagraf®** (**Extended** Release), **Envarsus®** (**Prolonged** Release), **Prograf®** (**Immediate** Release) (see Appendix 2)
      - These dosage forms are **NOT interchangeable**
    - Starting dose (rounded to nearest 1 mg)
      - Advagraf 0.15 mg/kg PO daily (first-line)
      - Envarsus 0.1 mg/kg PO daily (first-line)
        - Higher bioavailability vs. Advagraf (Advagraf:Envarsus conversion 1:0.7)
        - See Appendix 2 for specific indications where Envarsus should be used in lieu of Advagraf
      - Prograf 0.075 mg/kg PO/NG BID (used only in rare cases, e.g. for feeding tubes, absorption issues)
      - Note: slightly lower doses advised for obese patients (BMI >30)
    - Doses subsequently adjusted based on trough levels (see Appendix 3)

        - Time to steady state after initiation of therapy or dose change for Advagraf: 3-5 days, Envarsus: 1-2 days (anecdotal/SMH experience)
        - Dosing schedule: Advagraf and Envarsus: 1000H, Prograf: 1000H and 2200H
    - Cyclosporine PO (Neoral®)
        - Starting dose (rounded to nearest 25 mg): 3 mg/kg PO BID
        - Doses subsequently adjusted based on C2 levels (see Appendix 3)
        - Dosing schedule: 08:00H, 20:00H; C2 level timing: 10:00H
    - Cyclosporine IV (Sandimmune® IV)
        - Tacrolimus IV is not given/available at SMH
        - Convert Advagraf to cyclosporine IV in a 1:25 mg ratio, splitting the dose BID (e.g. Advagraf 6 mg PO daily = cyclosporine 75 mg IV BID)
        - Doses subsequently adjusted based on trough levels (see Appendix 3)
- Antimetabolite (mycophenolate>azathioprine)
    - Mycophenolate
        - Preferred formulation: enteric-coated mycophenolate sodium (Myfortic®)
        - Starting dose: Myfortic 360 mg PO QID (for GI tolerability), later converted to 720 mg PO BID upon Self Medication teaching (see page 5)
        - Myfortic is NOT interchangeable with mycophenolate mofetil (CellCept®)
            - Myfortic 360 mg = CellCept (PO/IV) 500 mg
    - Azathioprine (Imuran®)
        - Rarely used
        - Starting dose (rounded to nearest 25 mg): ~1.5 mg/kg daily
- Prednisone (all patients except prednisone-free protocol)
    - Dosing (rounded to nearest 5 mg): following methylprednisolone doses, prednisone 1 mg/kg PO daily x 5 days, then prednisone 0.5 mg/kg PO daily x 7 days, then 20 mg PO daily x 14 days (tapered to eventual 5 mg daily in Transplant Clinic)
- For PO to IV conversions, see Appendix 4

<u>OPPORTUNISTIC INFECTION PROPHYLAXIS</u>:

- PJP Px
    - Given for 1 year post-transplant
    - Therapeutic alternatives
        - First-line: cotrimoxazole (Septra® Single Strength) 400/80 mg PO MWF
        - Second-line (e.g. if sulfa allergy, anemia, leukopenia, transaminitis): atovaquone 1500 mg (10 mL) PO daily
        - Alternate second-line (e.g. if sulfa allergy): dapsone 100 mg PO daily (must check for G6PD deficiency)
- CMV Px
    - Valganciclovir (Valcyte®)
        - Indicated for CMV D+/R- (i.e. CMV mismatch) or R+ receiving ATG induction
        - Target doses and duration
            - CMV mismatch (**high risk**): 450 mg daily x 6 months
            - CMV R+ with ATG induction (**intermediate risk**): 450 mg daily x 3 months
            - Example dose adjustments in cases of delayed graft function (DGF)

eGFR/CrCl (mL/min)	Dose Adjustments for Kidney Dysfunction
≥40	450 mg once daily
25 to <40	450 mg every 2 days
10 to <25	450 mg twice weekly
<10 or dialysis	100 mg 3 times weekly (oral suspension) or 450 mg once weekly (if oral suspension unavailable)

        - Started on POD#3 (but may be further delayed if low risk)
        - Formulations: 450 mg tablet, liquid suspension
        - Doses should be given with a meal to improve absorption (e.g. QDinner at 1700H)

PRE/POST-OP ANTIBIOTICS:

- Most patients: cefazolin 1-3 g IV x 1 on call to OR
  - <80 kg: 1 g, >80 kg: 2 g, >120 kg: 3 g
- Patients with IgE-mediated penicillin allergy or cephalosporin allergy, or MRSA colonized patients: vancomycin 15 mg/kg (rounded to nearest 250 mg) IV x 1 dose pre-op (started on 8CS)
- Positive donor cultures (urine, blood, or Pseudomonas in BAL): broad spectrum antibiotics for ≥7 days
- If PD patient ordered post-op antibiotics and CATHETER REMAINS IN SITU, ensure Nystatin ordered for duration of antibiotic therapy + 7 days after cessation of antibiotic therapy

ADDITIONAL THERAPIES:

- GI Px: pantoprazole 40 mg PO daily (if patient previously taking a different PPI, OK to continue home PPI)
- VTE Px: dalteparin 5000 units SUBCUT daily (2500 units if <50 kg, 7500 units if >100 kg), usually ordered a few days post-op

POST-TRANSPLANT FLUID REPLACEMENT:

- Using low chloride balanced crystalloid in lieu of NS may reduce incidence of DGF (BEST-Fluids trial)
- Pending formulary review of Plasmalyte, **use Ringers Lactate for replacement of urine losses**

SELF MEDICATION PROGRAM:

All new kidney transplant recipients must demonstrate an ability to adhere to their new medications prior to discharge. The transplant pharmacist provides medication teaching, usually on POD#2-4.

Medications included for teaching in Self Medication Program include:

- Maintenance immunosuppression (CNI, antimetabolite, and prednisone)
- Supplemental therapies: PJP Px, CMV Px (if indicated), GI Px

During medication teaching, patients are provided the following:

- 7-day supply (+/- few days as per discretion of 8CS RPh) of Self Medications in vials, filled in IPS using Self Meds PPO
  - These medications are no longer sent with cart fill, as patients have their own supply on hand
- Medication calendar (see Appendix 7 for example)
- Patient education materials (medication information pamphlet, safe handling of medications pamphlet)

After medication teaching is complete, the patient will prepare and take their medications from their own “Self Medication” supply under RN supervision. 8CS RPh will refill supply weekly if required.

ESTIMATION OF KIDNEY FUNCTION POST-TRANSPLANT:

- New race-free eGFR equation for kidney transplant recipients (Raynaud et al, BMJ, 2023)
  - Fundamental differences between a single, denervated, transplanted kidney vs. two native kidneys with respect to SCr metabolism (due to the catabolic effects of steroids, recurrent infections, and rejection episodes leading to reduced muscle mass) and excretion (impaired in the presence of ATN, chronic rejection, and drugs such as Septra)
  - The equation (below) has been validated in multiple large international cohorts of kidney transplant patients and has been shown to perform better than the current GFR equations

$$eGFR = e^{4.4275492 - 0.8230475 \times \ln(\text{creatinine in mg/dL}) - 0.0124264 \times \text{creatinine}^2 \text{ in mg/dL} - 0.0055068 \times \text{age in years} + 0.1806494 \text{ (if patient is male)}}$$

  - You can use the online application for practical use (takes SCr values in umol/L)
- Please note that estimation of kidney function in the immediate post-transplant period is dynamic and challenging
  - If SCr decreasing, eGFR/CrCl value is likely underestimated

MEDREC/PRE-TRANSPLANT MEDS ASSESSMENT:

- HOLD dialysis medications (phosphate binders, ESA, calcitriol, cinacalcet, Replavite)
  - Resumed later only in cases of DGF
  - Calcitriol continued only if prior parathyroidectomy

    - Cinacalcet may be resumed in Transplant Clinic
- HOLD statins (resumed at discharge)
- HOLD ASA/antiplatelet until stable graft function (cleared by Nephrology & Urology)
- HOLD anticoagulation until stable graft function (cleared by Nephrology & Urology +/- Heme)
- HOLD ACEI/ARB (resumed 1-3 months post-transplant)
- CONTINUE beta-blockers (may use smaller dose)
- CONTINUE antihypertensives depending on BP (may use smaller dose)
- CONTINUE insulin (may initiate at smaller dose)
- Most other medications can be resumed on POD#1

TREATMENT OF HYPERTENSION IN IMMEDIATE POST-TRANSPLANT PERIOD:

- Continuation of pre-transplant medications, except ACEI/ARB (held x 1-3 months post-transplant)
- First-line new agent: **amlodipine**
- Subsequent new agents: alpha-blocker, hydralazine, beta-blocker, minoxidil
- Note: may be caused by fluid overload and treated with furosemide

TREATMENT OF STEROID-INDUCED HYPERGLYCEMIA AND POST-TRANSPLANT DM:

- Continuation of pre-transplant medications
    - Intensification of insulin regimen
- Addition of insulin NPH (usual starting dose: 10 units OR 0.2-0.4 units/kg) daily at the same time as prednisone (08:00H), to be titrated according to the patient's blood sugars
- If CrCl/eGFR >45: metformin (suggest starting dose 250 mg BID CC for avoidance of GI disturbance)
- Post-discharge: SGLT2i, GLP-1 agonist

COMMON DRUG INTERACTIONS:

- CNI drug interactions: see Appendix 1
- Myfortic: separate from Almagel/Maalox (but does **not** need to be separated from iron, calcium, magnesium)
- Cellcept: reduced exposure with PPIs & other acid-lowering therapies (does **not** need to be separated from iron)
- Lokelma: separate from other meds by at least 2 hours

MEDICATIONS TO AVOID IN TRANSPLANT PATIENTS:

- NSAIDs
- Interacting medications, unless benefit >> risk (see Appendix 1)
- Probiotics (risk of disseminated infection)
- Immune-stimulating drugs (e.g. NHPs and supplements)

LIVING DONOR ABOI TRANSPLANT:

- Desensitization
    - Rituximab 375 mg/m^2 IV x 1 dose 4 weeks prior to transplant (given in apheresis)
        - Pre-medications, given 30 min prior to infusion and Q4H PRN:
            - Acetaminophen 650 mg PO x 1
            - Diphenhydramine 50 mg IV x 1
            - Methylprednisolone succinate 50 mg IV x 1
        - Initiate infusion at a rate of 50 mg/hr, increasing the infusion rate by 50 mg/hr every 30 minutes, to a maximum of 400 mg/hr. Interrupt the infusion if any infusion reactions. Restart the infusion at one-half the previous rate upon resolution of symptoms
    - Immunoadsorption
        - Patients on ACEI/ARB must stop therapy one week prior to the first immunoadsorption treatment (risk of anaphylaxis)
- Pre-op IS (started 1 week prior to transplant)
    - Tacrolimus (Advagraf® 0.15 mg/kg daily OR Envarsus® 0.1 mg/kg daily), plus
    - Enteric-coated mycophenolate sodium (Myfortic®) 720 mg BID, plus
    - Prednisone 30 mg PO daily to be initiated 1 week prior to transplant
- Induction: basiliximab or ATG +/- IVIG (if baseline titre ≥1:128)
- Post-op IS: as per usual protocol

SECTION 2: TRANSPLANT REJECTION

GRAFT BIOPSY:

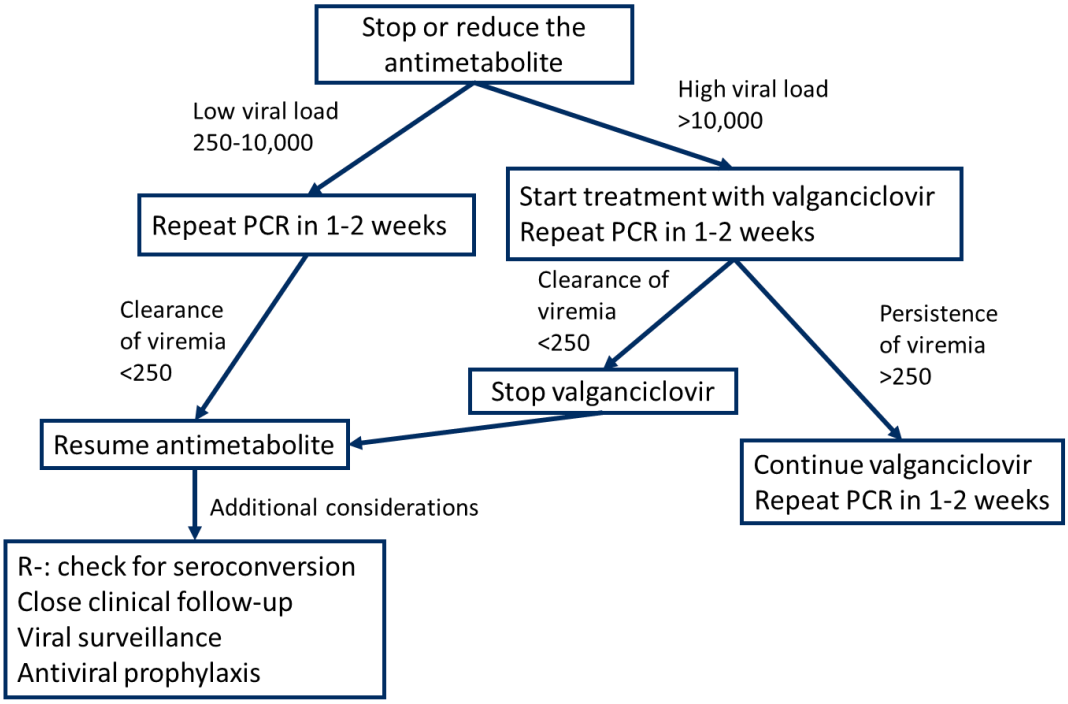
- Transplant patients may require kidney biopsies in the following situations:
  - Delayed graft function post-transplant
  - Prior transplant with suspected rejection +/- primary disease recurrence
- Procedure considered high risk of bleeding
- Pre-biopsy orders (to reduce post-biopsy bleeding):
  - Desmopressin acetate (DDAVP) 20 mcg IV x 1 to be given 30-60 minutes prior to renal biopsy
    - Given to reduce post-biopsy bleeding
    - Entered as "As Directed x 1" with Max # Doses = 1
    - Floor stock on 8CS
  - Intensification of antihypertensive regimen
  - Anticoagulation/antiplatelet held (see Thrombosis Canada DOAC and antiplatelet perioperative management guides)
    - Antiplatelet held x 5-7 days pre-biopsy
    - Warfarin held x 5 days pre-biopsy
    - Rivaroxaban, apixaban, and edoxaban held x 3 days pre-biopsy
    - Dabigatran held x 3-5 days pre-biopsy (depending on kidney function)
    - LMWH held x at least 24 hrs
    - VTE Px held x evening prior to biopsy

TREATMENT OF REJECTION:

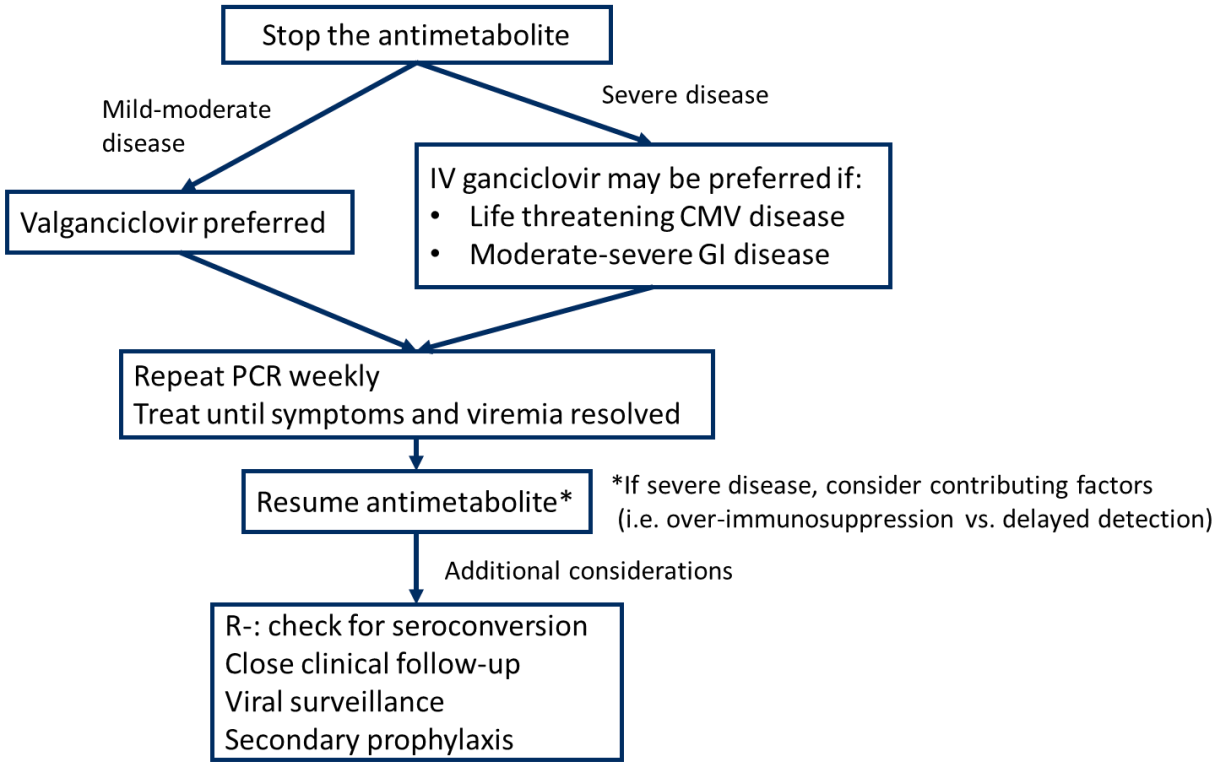
- Rejection should be confirmed by kidney biopsy (see above), but empiric treatment with steroids may be started pre-biopsy in some cases
- Treatment options (treatment decisions to be guided by kidney biopsy results):
  - Steroid pulse, usually methylprednisolone 500-1000 mg (or 5 mg/kg) IV daily x 3 days, followed by prednisone taper (usually 100 mg PO daily x 1 dose, 75 mg PO daily x 1 dose, 50 mg PO daily x 1 dose, then reduce by 5 mg daily until 20 mg daily ongoing, to be further tapered in Transplant Clinic)
  - +/- Thymoglobulin
    - Dosing: **Usual initial dose is 1 mg/kg or less**. Thereafter, **usual daily dose for treatment of rejection is 2 mg/kg**, for total **cumulative dose of ~5-6 mg/kg.**
      - As with induction treatment, a smaller first dose (e.g. 50 mg) is preferred to reduce incidence of cytokine release syndrome
      - Dose reassessed daily based on WBC and platelets: reduce dose by 50% if WBC 2-3 or platelets 50-75, hold if WBC <2 or platelets <50
    - Should be administered via central line if catheter in place or poor venous access, otherwise to be administered peripherally
  - +/- PLEX
  - +/- IVIG
- Opportunistic infection prophylaxis & additional therapies
  - Steroids
    - PJP Px: Septra SS MWF
    - GI Px: pantoprazole 40 mg daily
  - +/- Thymoglobulin
    - CMV Px: valganciclovir 450 mg daily (most patients)
      - See page 4 for dose adjustments in kidney dysfunction

SECTION 3: TREATMENT OF CMV INFECTION

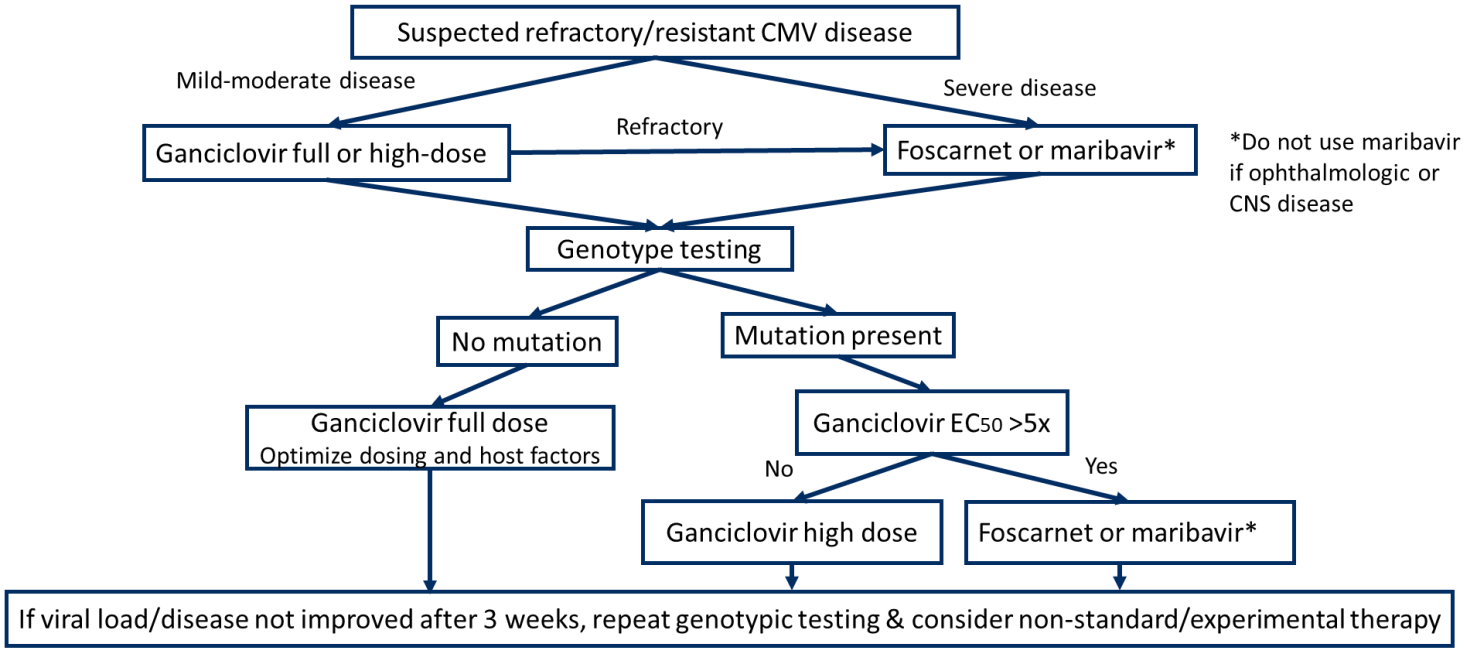
TREATMENT STRATEGY: ASYMPTOMATIC VIREMIA



TREATMENT STRATEGY: CMV DISEASE



TREATMENT STRATEGY: REFRACTORY/RESISTANT CMV DISEASE



CMV TREATMENT: THERAPEUTIC ALTERNATIVES

Drug	Treatment Dosing	Comments
Valganciclovir (PO)	900 mg PO BID	• Covers other herpesviruses • Risk of leukopenia • Requires renal dose adjustment
Ganciclovir (IV)	Full dose: 5 mg/kg IV Q12H High dose: 10 mg/kg IV Q12H	
Maribavir (PO)	400 mg PO BID	• Used for Does not cross blood-brain barrier • Drug interactions (P-gp & CYP 3A4 inhibitor)
Foscarnet (IV)	60 mg/kg IV Q8H or 90 mg/kg IV Q12H	• Highly nephrotoxic • Electrolyte wasting
Cidofovir (IV)	5 mg/kg Qweekly x 2, then Q2weeks thereafter	• Highly nephrotoxic • Fanconi syndrome • Ocular toxicity • Cross-resistance with ganciclovir

VALGANCICLOVIR: RENAL DOSE ADJUSTMENTS (TREATMENT DOSING)

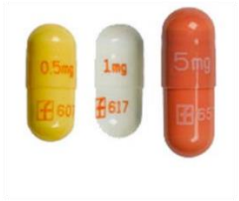
eGFR/CrCl (mL/min)	Dose
≥60	900 mg PO BID
40 to <60	450 mg PO BID
25 to <40	450 mg PO daily
10 to <25	450 mg PO Q2Days
<10 or dialysis	200 mg 3x/week (oral suspension)

APPENDIX 1: COMMON DRUG INTERACTIONS WITH CALCINEURIN INHIBITORS

Category	Drug	Interaction	Clinical Comments
Anticonvulsants	Carbamazepine	↓CSA/TAC/sirolimus levels, increased risk of rejection	Monitor CSA/TAC/sirolimus levels, dose adjustments required
	Phenobarbital		
	Phenytoin		
	Phenytoin	Additive gingival hyperplasia (cyclosporine only)	Good dental/oral hygiene with regular dentist visits
Antibiotics	Aminoglycosides (amikacin, gentamicin, tobramycin)	Additive nephrotoxicity	Avoid unless benefit >> risk; Monitor serum creatinine
	Caspofungin	↓TAC levels (tacrolimus only)	Monitor TAC level closely following addition, dose change, or discontinuation
	Clarithromycin, erythromycin	↑CSA/TAC/sirolimus levels, increased risk of toxicity	Avoid combination due to potential for dangerously high CSA/TAC/sirolimus levels
	Rifampin > rifabutin	↓ CSA/TAC/sirolimus levels, increased risk of rejection	Consult ID physician; Monitor CSA/TAC/sirolimus levels; Dose adjustments often required
	Vancomycin	Additive nephrotoxicity	Avoid unless benefit >> risk; Monitor serum creatinine
Antifungals	Amphotericin B	Additive nephrotoxicity	Avoid unless benefit >> risk; Monitor serum creatinine
	Fluconazole	↑ CSA/TAC/sirolimus levels, increased risk of toxicity	Monitor CSA/TAC/sirolimus levels; Dose adjustments often required
	Itraconazole	↑ CSA/TAC/sirolimus levels, increased risk of toxicity	↑ CSA/TAC/sirolimus levels, increased risk of toxicity
	Ketoconazole		
Antidepressants	Fluoxetine, fluvoxamine	↑ CSA/TAC/sirolimus levels, increased risk of toxicity	Consider alternatives (citalopram, escitalopram); Monitor CSA/TAC/sirolimus levels following addition, dose change, or discontinuation
Gout Therapies	Allopurinol and febuxostat if taking azathioprine (Imuran)	Azathioprine toxicity (leukopenia, thrombocytopenia, anemia)	**DO NOT** co-prescribe allopurinol with azathioprine
Cardiovascular medications	Diltiazem, verapamil	↑ CSA/TAC/sirolimus levels, risk of toxicity	Monitor CSA/TAC/sirolimus levels closely following addition, dose change, or discontinuation; Dose adjustments often required
	Amiodarone		
	Nifedipine (with cyclosporine)	Additive gingival hyperplasia	Avoid long-term use if possible; Good dental/oral hygiene with regular dentist visits
	Digoxin	↑ digoxin levels and half-life ↓ digoxin volume of distribution	Initiate low dose and follow up with serum digoxin levels; Closely monitor for symptoms of digoxin toxicity
GI medications	Cimetidine	↑ CSA/TAC/sirolimus levels, risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition/discontinuation
HIV Protease Inhibitors	Ritonavir, nelfinavir, cobicistat	↑ CSA/TAC/sirolimus levels, risk of toxicity	Consult ID physician; Use alternate therapy
Hormones	Oral contraceptives	↑ CSA/TAC/sirolimus levels, risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition/discontinuation
	Danazol		
HMG-CoA Reductase Inhibitors	Statins	↑ risk of myopathies and rhabdomyolysis	Use low doses, educate patient about myalgias, monitor LFTs
Others	NSAIDs (e.g. ibuprofen, naproxen), COX-2 inibitors	Additive nephrotoxicity	Recommend acetaminophen for over-the-counter pain management; Topical Voltaren may be used for short periods

APPENDIX 2: TACROLIMUS FORMULATIONS

TACROLIMUS FORMULATIONS:

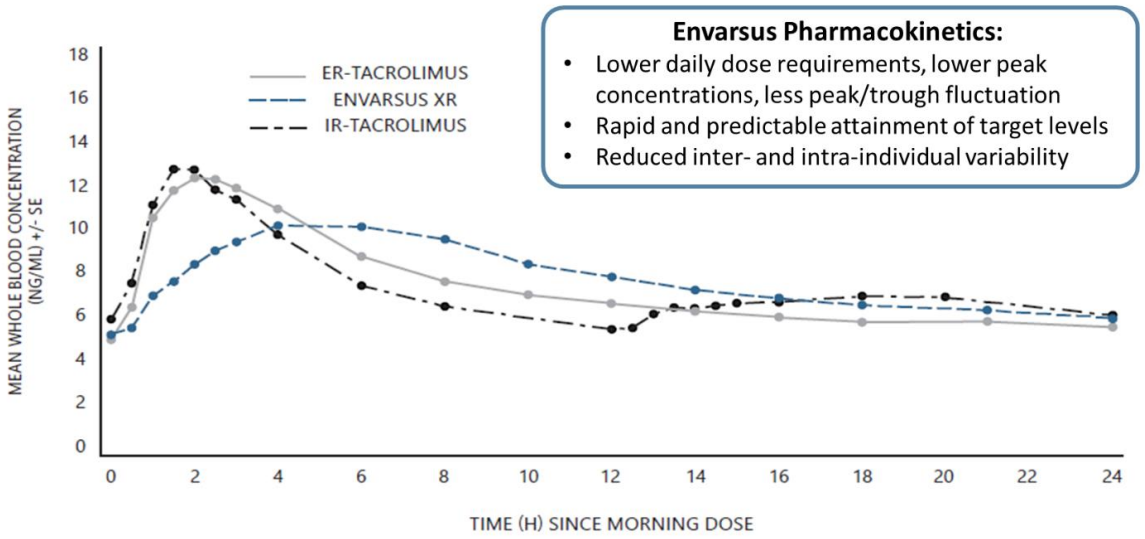


Prograf®
Tacrolimus IMMEDIATE Release

Advagraf®
Tacrolimus EXTENDED Release

Envarsus®
Tacrolimus PROLONGED Release

PHARMACOKINETICS OF TACROLIMUS:



ENVARSUS:

- Clinical benefits
  - Reduced tremor (Langone et al, 2015)
  - Improved kidney function in fast metabolizers of tacrolimus (Tholking et al, 2022)
  - Improved kidney function in liver transplant recipients (von Einsiedel et al, 2020)
  - At least as effective as Tac IR (Bunnapradist et al, 2016)
    - Significantly less treatment failure in black and elderly KTRs
- Additional benefits
  - Lower dose requirements (less pills, lower cost)
  - Flexible Patient Support Program which provides financial assistance to patients (e.g. for deductibles, co-payments, insurance maximums, gaps in coverage)
- Indications
  - De novo (inpatient setting)
    - First-line, as with Advagraf (choose one)
    - **Please consider use over Advagraf in the following cases:**
      - **Rapid metabolizer profile** (i.e. patients of African descent)
      - **Baseline tremor** (e.g. Parkinson's, essential tremor)
      - **Gaps in drug coverage** (e.g. private insurance <100%, Trillium, no insurance)
  - Switch (inpatient or clinic setting)
    - Observed rapid metabolizer/poor absorber: difficulty attaining therapeutic Tac levels on Advagraf despite dose escalation, or high dose requirements (e.g. >/=15 mg)
    - Observed tremor
    - Drug coverage issues
- Should NOT be used in patients with:
  - Prior bowel resections/colectomy
  - Feeding tubes

Tacrolimus (FK 506) Therapeutic Drug Monitoring

- Requires whole blood samples
- Formulations of tacrolimus: **Advagraf®** (**Extended** Release), **Envarsus®** (**Prolonged** Release), **Prograf®** (**Immediate** Release)
- Dosing schedule: Advagraf® and Envarsus®: 1000H, Prograf®: 1000H and 2200H
- Time to steady state after initiation of therapy or dose change for extended release products (Advagraf®, Envarsus®): 3-5 days
- Advagraf®:Prograf® conversion = 1:1 (i.e. Advagraf® 10 mg = Prograf® 5 mg BID)
- Advagraf®/Prograf®:Envarsus® conversion = 1:0.7 (i.e. Advagraf® 10 mg = Envarsus® 7 mg)

PO tacrolimus, all brands: C0 (trough level immediately prior to next dose)

	Usual target (mcg/L)
Most patients *regardless of time out from transplant*	5-8
Prednisone-free protocol	6-9

- Levels slightly outside this range may be acceptable for some patients

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Cyclosporine Therapeutic Drug Monitoring

- PO dosing schedule: 0800H and 2000H
- IV dosing schedule: intermittent infusion, BID
- IV:PO cyclosporine conversion = 1:3 (i.e. cyclosporine 150 mg PO BID = cyclosporine 50 mg IV BID)
- Advagraf®:IV cyclosporine conversion: 1:25 (i.e. Advagraf® 6 mg PO daily = cyclosporine 75 mg IV BID)

PO cyclosporine: C2 (concentration at 2 hours post-dose, i.e. 1000H)

Time Out From Transplant	**Target C2 Level (mcg/L)**
0–30 days	900–1100
1–3 months	800–1000
3–12 months	600–900
>12 months	300–800

IV cyclosporine: C0 (trough level immediately prior to morning dose)

Time Out From Transplant	**Target C0 Level (mcg/L)**
0–30 days	350–450
1–3 months	300–350
3–6 months	250–300
6–12 months	200–250
>12 months	100–200

APPENDIX 4: PO TO LIQUID/IV DOSE CONVERSIONS

Tacrolimus:

- Tacrolimus Extended Release (Advagraf®) is the preferred calcineurin inhibitor for most transplant recipients
- **BETWEEN TACROLIMUS PO FORMULATIONS:**
  - Advagraf® (**Extended** Release) to Prograf® (**Immediate** Release): Convert in a 1 : 1 ratio, splitting the dose BID (e.g. Advagraf® 6 mg PO daily = Prograf® 3 mg PO BID)
  - Advagraf® (**Extended** Release) to Envarsus® (**Prolonged** Release): Convert in a 1 : 0.7 mg ratio, to be given once daily (e.g. Advagraf® 10 mg PO daily = Envarsus® 7 mg PO daily)
  - Only Prograf® is commercially available as a liquid or IV
- **ORAL LIQUID REQUIRED:**
  - Convert Advagraf® (**Extended** Release) to Prograf® (**Immediate** Release) Liquid in a 1 : 1 ratio, splitting the dose BID (e.g. Advagraf® 6 mg PO daily = Prograf® Liquid 3 mg PO/NG BID)
- **IV REQUIRED:**
  - Tacrolimus IV is not given/available at SMH
  - Convert Advagraf® to cyclosporine IV in a 1 : 25 mg ratio, splitting the dose BID (e.g. Advagraf® 6 mg PO daily = Cyclosporine 75 mg IV BID)

Cyclosporine:

- **IV REQUIRED:**
  - Convert PO cyclosporine to IV cyclosporine in a 3 : 1 ratio (e.g. cyclosporine 150 mg PO BID = cyclosporine 50 mg IV BID)

Mycophenolate:

- Mycophenolic acid sodium (Myfortic®) is the preferred antimetabolite for most transplant recipients
- **BETWEEN MYCOPHENOLATE PO FORMULATIONS:**
  - Myfortic® 360 mg = CellCept® (mycophenolate mofetil) 500 mg
- **ORAL LIQUID REQUIRED:**
  - Convert Myfortic® 360 mg to CellCept® Liquid 500 mg (e.g. Myfortic® 720 mg PO BID = CellCept® Liquid 1000 mg PO/NG BID)
- **IV REQUIRED:**
  - Convert Myfortic® 360 mg to CellCept® IV 500 mg (e.g. Myfortic® 720 mg PO BID = CellCept® 1000 mg IV BID)
  - CellCept® IV is 100% bioavailable

Prednisone:

- **IV REQUIRED:**
  - Convert prednisone to methylprednisolone in a 5 : 4 ratio (e.g. prednisone 50 mg PO daily = methylprednisolone 40 mg IV daily)

Developed By: Lucy Chen, RPh (July 24, 2013)
Updated By: Vivian Tsoi, RPh (December 9, 2020)

References: CPS (Drug Monographs), SMH Transplant Physicians

APPENDIX 5: DISCHARGE PRESCRIPTIONS

For each medication, MUST select one of the following options:

- DO NOT CONTINUE → REASSESS or STOPPED
- CONTINUE
    - If a home medication matches the hospital medication ordered, select CONTINUE HOME MEDICATION (no Rx required in this case)
    - If a home medication matches the hospital medication ordered, but there is a change in dose or frequency intended to be continued post-discharge, select CONTINUE HOSPITAL MEDICATION (Rx REQUIRED in this case)
    - If NEW medication ordered in hospital and intended to be continued post-discharge, select CONTINUE HOSPITAL MEDICATION (Rx REQUIRED in this case)

If Rx required:

- Usual quantity (capsules or tablets): 1 month, 0 refills
- Liquids (e.g. atovaquone, Nystatin): 1 bottle
- Insulins: 1 box of pens
    - Note: Lantus®, Humalog®, and Novorapid® are NO LONGER covered for ODB patients and should be changed to the biosimilar version (see Appendix 5)
- Antibiotics: indicate days left to complete (e.g. 5 days) and can enter dates in Instructions (e.g. Jan 1-5 inclusive)
- LU codes: see APPENDIX 6
- The final Rx should be FAXED to the patient's pharmacy

APPENDIX 6: COMMON POST-TRANSPLANT LU CODES

NAME	LU CODE	COMMENTS/LU CRITERIA
IMMUNOSUPPRESSANTS		
Cyclosporine **(NEORAL®)**	None	BRAND NAME covered ONLY if prescription is filled at SMH outpatient pharmacy
Sirolimus **(RAPAMUNE®)**	392	For both liquid suspension and capsules
Tacrolimus Immediate Release **(PROGRAF®)**	173	For both liquid suspension and capsules
Tacrolimus Extended Release **(ADVAGRAF®)**	410	
Tacrolimus Prolonged Release **(ENVARSUS®)**	590	
Mycophenolate sodium **(MYFORTIC®)**	None	
Mycophenolate mofetil (tablet) **(CELLCEPT®)**	None	
Mycophenolate mofetil (liquid) **(CELLCEPT® liquid suspension)**	556	
ANTI-INFECTIVES		
Valganciclovir (tablet) **(VALCYTE®)**	568	For CMV prophylaxis only For CMV treatment: contact EAP TRS*
Valganciclovir (liquid) **(VALCYTE® liquid suspension)**	572	
Atovaquone (liquid) **(MEPRON®)**	None	
Dapsone	None	Check G6PD prior to initiation
Valacyclovir **(VALTREX®)**	None	
OTHER MEDICATIONS		
Proton Pump Inhibitors	293	Pantoprazole, lansoprazole, omeprazole
	None	Rabeprazole
Ezetimibe **(EZETIMIBE®)**	380	In combination with a statin in patients not reaching LDL targets despite use of max tolerated doses
	381	Monotherapy in patients not tolerating statin therapy
Filgrastim (G-CSF) (pre-filled syringe) **(GRASTOFIL®)**	None	300 mcg (1st course) or 480 mcg (2nd course) SUBCUT daily x 3 days CBC approx. 7 days after last filgrastim dose Use **NEUPOGEN** vials if documented Latex Allergy
Filgrastim (G-CSF) (vial) **(NEUPOGEN®)**	501	For documented Latex Allergy Same dosing as **GASTROFIL®**
Insulin Aspart **(TRURAPI®)** Insulin Lispro **(ADMELOG®)** Insulin Glargine **(BASAGLAR®)**	None	**NOVORAPID®, HUMALOG®,** and **LANTUS®** are no longer covered by ODB
Ferric Derisomaltose, or Iron Isomaltoside **(MONOFERRIC®)**	610	Dilute 1000-1500 mg in 100-250 mL sodium chloride 0.9%. Infuse 1000 mg over 60 minutes and 1500 mg over 90 minutes.

Can't find what you are looking for? Go to www.healthinfo.moh.gov.on.ca/formulary/

*Exceptional Access Program (EAP) Telephone Request Service: 416-327-8109

ST. MICHAEL'S UNITY HEALTH TORONTO

Name: IPS Example Date: August 1, 2024

Time	Picture	Medication & Instructions	Reason	Thurs Aug 1	Fri Aug 2	Sat Aug 3	Sun Aug 4	Mon Aug 5	Tues Aug 6	Wed Aug 7
Morning (with food) 8 am	 50 mg  5 mg	**Prednisone** Aug 1-5: Take **70 mg** (**1 x 50 mg** tablets and **4 x 5 mg** tablets) once daily with food Aug 6-12: Take **35 mg** (**7 x 5 mg** tablets) once daily with food Starting Aug 13: Take **20 mg** (**4 x 5 mg** tablets) once daily with food until further notice	Anti-Rejection							
Morning 10 am		**Tacrolimus PROLONGED Release (Envarsus®)** Take ___ **mg** (___ **x 4 mg** tablets AND ___ **x 1 mg** tablets) once daily **Dose to be adjusted based on drug level* ***On bloodwork days, take AFTER blood test*	Anti-Rejection							
Morning 10 am		**Mycophenolate (Myfortic®)** Take 720 mg (2 tablets) twice daily	Anti-Rejection							
Morning 10 am		**Pantoprazole (Pantoloc®)** Take 40 mg (1 tablet) once daily	Stomach Protection							
Morning 10 am		**Cotrimoxazole (Septra®/Sulfatrim® Single Strength)** Take 400/80 mg (1 tablet) on Mon, Wed, and Fri	Infection prevention	None today		None today	None today		None today	
Dinner (with food) 5 pm		**Valganciclovir (Valcyte®)** Take 450 mg (1 tablet) once daily with food	Infection prevention (CMV)							
Bedtime 10 pm		**Mycophenolate (Myfortic®)** Take 720 mg (2 tablets) twice daily	Anti-Rejection							

APPENDIX 8: ADDITIONAL RESOURCES

PRE-OP AND POST-OP KIDNEY TRANSPLANT ORDER SETS

- Soarian → orders → search “transplant”
- Soarian → orders → specialty → Nephrology

THYMOGLOBULIN ORDER SET

- Soarian → orders → search “thymo”

CLINICAL TIP SHEETS

- CNI Monitoring document
- PO to oral liquid/IV conversion for renal transplant medications
- Thymoglobulin info sheet

WORKSHEETS

- Sterile worksheets (IV)
  - Azathioprine
  - Basiliximab
  - Cyclosporine
  - Ganciclovir
  - Mycophenolate
  - Thymoglobulin
- Hazardous NG worksheets
  - Azathioprine
  - Mycophenolate
  - Sirolimus
  - Tacrolimus
  - Valganciclovir

EXTERNAL RESOURCES

- BC Transplant Medication Guidelines for Solid Organ Transplants
- Canadian Society of Transplantation
- KDIGO
- CMV Guidelines
  - The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation (Kotton et al, *Transplantation*, 2018)
  - Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice (Razonable et al, *Clinical Transplantation,* 2019)