MOTP CLINICAL DIRECTIVES

Program:	Kidney and Pancreas Transplantation			**Section:**	Recipient Management		
Title:	**Immunosuppressive Regimen for Kidney Transplant Recipients**						
Approved by:	Kidney Transplant Team						
Original Issue:	2014/May/05	**Version #:**	3	**Last Revision:**	2020/Apr/21	**Last Review:**	2020/Mar/13

Living Donor					
Recipient	**Thymoglobulin**	**Basiliximab (Simulect)**	**Calcineurin Inhibitor**	**Myfortic**	**Steroids**
Low immunological risk recipient		20 mg IV Day 0 (pre-op, within 2 hours of O.R) *and* Day 4	Advagraf 0.15 mg/kg, once daily (morning dosing) In rare cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
High immunological risk recipient	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually Day 4 - 5) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk		Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
HLA Haplo Identical		20 mg IV Day 0 (pre-op, within 2 hours of O.R) *and* Day 4	Advagraf 0.15 mg/kg, once daily (morning dosing) Refer to Journal Club Summary Paper (Jan 2019)	Myfortic 720 mg q12h	Protocol

Deceased Donor					
Treatment options should be considered the same for NDD & DCD donors. Immunosuppressive decisions should be based on DGF risk and recipient immunological risk.					
Recipient	**Thymoglobulin**	**Basiliximab (Simulect)**	**Calcineurin Inhibitor**	**Myfortic**	**Steroids**
SCD Low immunological risk recipient		20 mg IV Day 0 (pre-op, within 2 hours of O.R) *and* Day 4	Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
SCD High immunological risk recipient	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually Day 4- 7) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk		Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
ECD Low or High immunological risk recipient	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually Day 4-7) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk Given to delay start of CNI +/- immunological risk	If Thymo cannot be used, Simulect is acceptable but **low threshold** for Thymo with immunologic risk or serial biopsies 20 mg IV Day 0 (pre-op, within 2 hours of O.R) *and* Day 4 Low threshold to convert to Thymo or add Thymo even after Simulect with severe or anticipated long Delayed Graft Function	Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
2nd Transplant No DSA	Not required unless previous transplant lost due to aggressive immune rejection	20 mg IV Day 0 (pre-op, within 2 hours of O.R) *and* Day 4			Protocol
2nd Transplant DSA	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually Day 5) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk				Protocol
Paediatric En Bloc Low or High immunological risk	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually to POD 4-7) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk; Given to delay start of CNI +/- immunological risk		Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
ABO Mismatch (i.e., A2 donors into B)	Not required unless other indications for Thymo exist		Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
High Risk (e.g., antibody rejection, high PRA, low background DSA, previous early loss, etc.)	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually to POD 4-7) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk; Given to delay start of CNI +/- immunological risk		Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol
Elderly patient >70 years	Use of Thymo in recipients >65 years of age should reflect careful consideration of true immune risk and any additional risk for specific infections If rejection and Thymo required, give ½ dose Thymo	Simulect preferred	Advagraf 0.15 mg/kg, once daily (morning dosing) In remote cases, when Tacrolimus/Prograf is used, the dosage is 0.15 mg/kg in divided doses given q12h	Myfortic 720 mg q12h	Protocol

Recipient	Thymoglobulin	Basiliximab (Simulect)	Calcineurin Inhibitor	Myfortic	Steroids
Steroid Avoidance	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk	**OR** 20 mg IV Day 0 (pre-op, within 2 hours of O.R) *and* Day 4	Advagraf 0.15 mg/kg, once daily (morning dose) See steroid avoidance protocol	Myfortic 720 mg q12h	See steroid avoidance protocol

Kidney-Pancreas Recipient					
Recipient	**Thymoglobulin**	**Basiliximab (Simulect)**	**Calcineurin Inhibitor**	**Myfortic**	**Steroids**
	1.5 mg/kg Pre-op/Intra-op then DAILY up to 7.5 mg /kg (usually Day 5) Adjust by CBC (see reference) Can be extended up to maximum dose of 10 mg/kg depending on immunological risk		Advagraf 0.15 mg/kg, once daily (morning dosing)	Myfortic 720 mg q12h	Protocol

Immunological Risk Categories for Recipients:

Low Immunological Risk

- First transplant
- cPRA <20%
- No Donor-Specific Antibody

High Immunological Risk

- Re-transplant with first transplant lost due to acute rejection
- Previous extra-renal transplant
- History of antibody-mediated rejection
- Presence of Donor-Specific Antibody – Class 1 +/or 2, Luminex >1000 MESF
- Flow crossmatch Positive (T cell)

HLA Haplo Identical Living Kidney Pair

Patients who receive kidneys from Haplo identical siblings are at lowest risk for rejection and should be tapered to lowest possible immunosuppressive therapy. Refer to Journal Club Summary Paper (Jan 2019)..

A2/A2B to B and O Recipients Transplant

- Not considered an increased immunological risk;
- Refer to A2/A2B to B and O Recipients Transplant Guidelines

Types of Donors:

Neurological Determination of Death (NDD)

Donation after Cardiocirculatory Death (DCD)

- can be SCD or ECD (see definitions below)
- highest risk of IF/TA; careful consideration of recipient required

Standard Criteria Donor (SCD)

- Age <60 with no ECD criteria

Expanded Criteria Donor (ECD)

- Donor age >60 years
  OR
- Donor age 50-59 with 2 of 3
  1. CVA as cause of death
  2. Pre-existing HTN
  3. Serum creatinine >132 umol/l

  Expanded Criteria Donor – at higher risk of interstitial fibrosis and tubular atrophy (IF/TA); careful consideration of recipient required. May choose to transplant en bloc if nephron mass is a concern. If kidney biopsy is required, the retrieval team should be notified and the biopsy performed in the donor OR.

Paediatric En Bloc

Paediatric donors are <4 years. Recipients of these kidneys are given Thymoglobulin induction with the hope of avoiding need for biopsy. If kidney biopsy is required, the transplant surgery team should be informed to perform the biopsy because of the increased technical challenges with two kidneys.

Exceptional Distribution:

- Is the release of cells, tissues, or organs to a transplant program from a donor in whom the donor suitability assessment has identified an increased risk for disease transmission?

Medications: (Further information can be found on the LHSC Pharmacy website.)

In addition to the following immunosuppressive medications, all patients are given:

- **PCP Prophylaxis for life**
  - Septra DS 1 tablet every Monday/ Wednesday/ Friday
  - Dapsone 100 mg OD if mild Septra allergy
  - Atovaquone 1500 mg daily if severe allergy to Septra (e.g. Anaphylaxis)
  - Pentamidine inhalation monthly x1 year if no other option appropriate. Requires EAP approval.
- **GI protection for first 3 months**
  Formulary PPI (Proton Pump Inhibitor) OD

1) Thymoglobulin (Polyclonal Anti-thymocyte Globulin)

Description

Polyclonal IgG from rabbits immunized with human thymocytes; adsorbed to reduce unwanted antibodies

Mechanism of Action

Blocks T-cell membrane proteins (CD2, CD3, CD45, and so forth), causing altered function, lysis, and prolonged T-cell depletion
Thymoglobulin is a rabbit-derived polyclonal anti-human thymocyte antibody

Indications

- Treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression
- Induction in adult renal transplant recipients who are high immunological risk
- Use of Thymo in recipients of DCD should be based on immunological risk. (Refer to Journal Club Summary Paper, Nov 2019)
- Use of Thymo in recipients >65 years of age should reflect careful consideration of true immune risk and any additional risk for specific infections

Contraindications

Thymoglobulin is contraindicated in patients with:

- History of allergy or anaphylaxis to rabbit proteins *or* patients with an anaphylaxis to previous Thymoglobulin administration
- An acute infectious illness

Side effects

- Cytokine-release syndrome (fever, chills); severe reaction may include hypotension, ARDS, pulmonary edema
- Arthralgias, skin rashes
- Serum sickness (may be seen by end of 1st week of treatment)
- Leucopenia
- Thrombocytopenia (rare)
- Anaphylaxis (rare)

Treatment of anaphylaxis

- Infusion should be terminated immediately.
- Treatment with epinephrine and other resuscitative measures including oxygen, IV fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated, should be provided.

Premedication

Pre-medication should be given 30-60 minutes prior to infusion

- Acetaminophen 650 mg po with sip

- Benadryl 50 mg IV
- The daily dose of steroids is usually sufficient and no further pre-medication dose is ordered.

Dosing

1.5 mg/kg Total Body Weight – Thymoglobulin is available in vials containing 25 mg. Whenever possible, the total daily dose should be a multiple of 25 to help reduce cost due to drug wastage. Drug is expensive so notify pharmacy immediately if there may be a change in dose or administration.

- Initial dose: Drug is sent to the OR with the patient; first dose is begun in the OR following insertion of central line and prior to reperfusion. Administered over 6-8 hours. A 0.22 micron in-line filter is used. A Baxter pump is used. Mix in 250cc 0.9% saline. Intra-operative thymoglobulin administration is associated with a significant decrease in DGF, better early allograft function and a deceased post-transplant hospital length of stay.
- Subsequent doses: Ordered daily based on bloodwork and administered in MOTU. Goal will be to target 6-8 mg/kg depending on reason for use and/or response to therapy. Absolute maximum dose is 10 mg/kg.
- May be given peripherally under extenuating circumstances (i.e., 1st dose; unable to insert PICC); Contact pharmacy for guidance.
- Monitoring: White blood cell and platelet counts should be monitored daily to assess the degree of neutropenia and thrombocytopenia.
- Dose Adjustment:

WBC count cells/mm^2	Platelet counts cells/mm^2	Thymoglobulin dose
>3,500	>80,000	Full dose
1,500 – 3,500	50,000 – 80,000	Reduce dose by 50%
<1,500	< 50,000	Stop or hold treatment

If lymphocyte count <0.1 may hold dose for 24 hours.

Need for co-administration of anti-viral therapy

- CMV prophylaxis:
  - IV ganciclovir followed by oral valganciclovir
  - Required for CMV-positive recipients (regardless of donor CMV status) and recipient induced with Thymoglobulin. – prophylaxis x 3 months
  - Required if recipient CMV negative and donor CMV positive, recipient will require CMV prophylaxis with IV ganciclovir followed by oral valganciclovir x 6 months.

  See *CST Consensus workshop on CMV management in solid organ transplantation final report (Am J Transplant 2005; 5: 218-227)*.

- EBV prophylaxis: If recipient EBV –ve, the recipient will require EBV prophylaxis x 6 months with IV ganciclovir as an inpatient followed by oral Valganciclovir with subsequent viral monitoring x 1 year. A written request must be submitted to the Exceptional Access Program (EAP) by the Consultant as soon as possible for patients with a government drug plan (ODB, Trillium, ODSP)

2) Basiliximab (Simulect®)

Description: Chimeric monoclonal antibody against CD25 (interleukin-2-receptor α chain)

Mechanism of action:

- Basiliximab binds to and blocks the interleukin-2 receptor α chain (CD25 antigen) on activated T cells inhibiting interleukin2-induced T-cell activation for 4 - 6 weeks. It is unlikely to be removed by dialysis.

Indications: Prophylaxis of acute organ rejection in renal transplant recipients

Contraindications: Known hypersensitivity to basiliximab, mouse cell proteins or any other component of the formulation

Side effects

- Overall, compared to other immunosuppressants, basiliximab is well tolerated and does not appear to add significantly to the background adverse event profile of the typical transplant patient.
- Hypersensitivity reactions (uncommon).

Dosing:

20 mg IV over 20 -30 minutes

- Living Donor Surgery
  - Administered upon determination that the transplant surgery will proceed.
  - First dose administered Pre-OR in the Surgical Preparation Unit within 2 hours of start of surgery.
  - Day 4 dose is given in the MOTU.
- Deceased Donor Surgery
  - Administered upon determination that the transplant will proceed.
  - First dose administered in MOTU or in the Operating Room within 2 hours of start of surgery.
  - Day 4 dose is given in the MOTU.

Need for co-administration of anti-viral therapy:

This is an area of controversy.

- CMV prophylaxis: CMV negative recipients who receive a CMV-positive kidney will require CMV prophylaxis with IV ganciclovir followed by oral valganciclovir x 6 months. See protocol. Ref. *CST Consensus workshop on CMV management in solid organ transplantation final report (Am J Transplant 2005; 5: 218-227).* If patient is CMV positive and induced with Simulect, no provincial drug coverage is currently available although anti-viral treatment is recommended.
- EBV prophylaxis: If recipient EBV –ve, the recipient will require EBV prophylaxis x 6 months with IV ganciclovir as an inpatient followed by oral valganciclovir in the outpatient setting. Subsequent viral monitoring x 1 year with EBV PCR, IgG, IGM. A written request must be submitted to the Exceptional Access Program (EAP) by the Consultant as soon as possible for patients with a government drug plan (ODB, Trillium, ODSP)

3) Calcineurin Inhibitor (Prograf® /Tacrolimus or Advagraf® (Tacrolimus MR))

Description: Macrolide antibiotic from Streptomyces tsukubaensis

Mechanism of action:

- Binds to FKBP12; complex inhibits calcineurin phosphatase and T-cell activation
- FK-FKBP complex binds to calcineurin and inhibits activation of IL-2
- Mechanism of action similar to cyclosporine, though it binds to a different immunophilin

Indications: Prophylaxis of acute organ rejection in renal transplant recipients; treatment of rejection

Contraindications: Known hypersensitivity to tacrolimus

Dosing:

- Unless induced with Thymoglobulin, start CNI on return from Operating Room
- If induced with Thymoglobulin, start CNI after last Thymo dose
- Advagraf® dose is 0.15 mg/kg but this is **once a day dosing**; cannot be administered via NG tube
- If Prograf® / tacrolimus is used, dose is 0.15 mg/kg/day given in divided doses q12 hour; liquid formulation available, which can be administered via NG tube
- Can be given by continuous IV infusion if unable to take orally (approximately ¼ of oral dose)
- Adjust dose depending on trough levels
- Trough levels determined by current HPLC/MS rather than previous methods are approximately 15-20% lower than previously reported and target levels should be based accordingly
- Note: Adjustment of dosage in patient receiving once/day formulation of tacrolimus (Advagraf) should be based on levels obtained at least 48 hours post dose change, in contrast to previous twice/day formulation (Prograf)
- Approximate goal for trough (C0) tacrolimus levels **as measured by HPLC levels**:

	Low risk:	**High risk or Steroid Avoidance (have a greater range)**
Month 0-3:	6.5 ± 0.5 ng/ml	7.0 ± 0.5 ng/ml
Month 3-6:	6.0 ± 0.5 ng/ml	6.5 ± 0.5 ng/ml
> 6 months	5.0 ± 0.5 ng/ml	6.0 ± 0.5 ng/ml

Note:

- Levels by Mass spec/HPLC, measuring only parent compound
- Levels for Prograf and Advagraf are considered equivalent
- High risk is defined by history of rejection, DSA (current or historic), use of Thymoglobulin for induction other than DGF (high PRA and risk of immune memory activation despite negative crossmatch). Chronic and stable patient levels need to be assessed on a case by case basis, but generally levels should be adjusted to be higher than 4 ng/ml unless concern of CNI toxicity or malignancy, particularly in those with less than normal MPA exposure.

- MPA trough levels can be considered in select adult patients, to achieve >1.5 ng/ml
- Patient with risk factors for Type II diabetes (strong family history, hepatitis C-positive recipient, African American, high BMI) should be informed during the transplant assessment process that the risk of developing diabetes is higher when tacrolimus is used and **Neoral® should be considered as primary calcineurin inhibitor**
- Many drug interactions

Adverse Effects:

- Similar to cyclosporine but with lower incidence of hypertension, hyperlipidemia, skin changes; higher incidence of post-transplant diabetes mellitus and neurotoxicity (tremor is more prominent)

4) Neoral® (cyclosporine)

Description: 11-amino-acid cyclic peptide from Tolypocladium inflatum

Mechanism of action: Binds to cyclophilin; complex inhibits calcineurin phosphatase and T-cell activation

Indications:

- Prophylaxis of solid organ rejection in allogeneic transplants
- Neoral should be considered as primary calcineurin inhibitor in patients with risk factors for Type II diabetes (strong family history, hepatitis C-positive recipient, African American, high BMI)

Contraindications: Hypersensitivity to cyclosporine or any of its constituents

Adverse Effects:

Nephrotoxicity, hemolytic-uremic syndrome, hypertension, neurotoxicity, gum hyperplasia, skin changes, hirsutism, post-transplant diabetes mellitus, hyperlipidemia

Dosing:

- Unless induced with Thymoglobulin, start CNI on return from Operating Room
- If induced with Thymoglobulin, start CNI after last Thymo dose
- Oral: Dose is 10 mg/kg/day in divided doses q12h
- IV: Can be given as a continuous (24 hour) IV infusion. Initially, 3-5 mg/kg/day IV (one-third the oral dose), given as a continuous infusion and titrated to blood level until oral therapy can be tolerated. Dose adjustment may be required on a daily or every-other-day basis.
- Adjust oral dose depending on C2 levels for first year. C2 cyclosporine blood concentration at 2 hours after administration. Sampling time with a deviation of +/- 15 minutes is acceptable. Recommended target +/- 20% window.
- Subsequent monitoring beyond 1 year is via trough levels.
- Many drug interactions

C2 levels

Months post-transplant	Target Level (C2) (ug)/l	Months post-transplant	Target Level (C2) (ug)/l
0-1 month	1700	4-6 months	1100
2 months	1500	7-12 months	900
3 months	1300	14+ months	800

New daily dose = Current daily dose x desired C2 target
Actual C2 level

C0 - Trough Levels
>1 year 50-150 ug/l

5) Mycophenolate Sodium (Myfortic®)

Description: Mycophenolic acid from Penicillium molds. Myfortic is enteric coated.

Mechanism of Action:
Mycophenolic sodium is a reversible and uncompetitive inhibitor of inosine monophosphate dehydrogenase thereby inhibiting the de novo synthesis pathway of the guanosine nucleotide without incorporation into DNA. It exerts a potent cytostatic effect on B and T lymphocytes by inhibiting de novo synthesis because it is a crucial pathway for proliferation.

Indications: Use in prophylaxis of rejection in renal transplant recipients

Contraindications: Hypersensitivity to mycophenolate sodium or any of its constituents

Adverse Effects: Gastrointestinal symptoms (mainly diarrhea), neutropenia, mild anemia

Dosing:
- May be given IV if unable to take orally, however it is very expensive. If IV dose is required, mycophenolate sodium will need to be converted to mycophenolate mofetil (CellCept).

Dose conversion - Mycophenolate

In some cases it may be necessary to convert patients between Mycopheonlate Mofetil (CellCept®) and Mycophenolate Sodium (Myfortic®). Dose ratios for conversion are presented in the table below:

Drug Name	Mycophenolate Mofetil		Mycophenolate Sodium
Brand Name	CellCept® Apo-Mycophenolate® Sandoz-Mycophenolate®		Myfortic®
Dosage Forms	Capsules Tablets Suspension Injection		Tablet
Dose conversions	250 mg	↔	180 mg
	500 mg	↔	360 mg
	750 mg	↔	540 mg
	1000 mg	↔	720 mg

Dose frequency should be maintained, for example:

250 mg **every 12 hours** of CellCept® ↔ 180 mg **every 12 hours** of Myfortic®

- Dose on return to unit
- Dose 720 mg every 12 hours
- Dose adjustment not required in liver dysfunction
- Dose adjustment is not necessary in patients with delayed renal graft function postoperatively. Not removed by Peritoneal Dialysis or Hemodialysis. Supplemental dosing is not necessary.
- For patients of African American, consider higher dosing
- For leukopenia / anemia/ infection, consider reduction of Myfortic
- For GI symptoms (GERD, nausea, vomiting, diarrhea), ensure patient is taking with food
    - Consider dose adjustment (example – smaller doses more frequently – 360 mg qid)
    - If dose adjustment ineffective, consider dose reduction, cessation or conversion to mycophenolate alternative
    - Exclude other causes of adverse effect (i.e., GI sepsis, other medications)
    - Avoid antacids containing aluminum and magnesium; calcium-based antacids (i.e. Tums) are safe to use
    - Avoid multivitamins with minerals (iron, zinc etc.); if using, must space at least 4 hours from mycophenolate sodium
- Blood level monitoring not required but may improve efficacy

Comment: Mycophenolate is associated with an increased risk of congenital malformations and first trimester pregnancy loss when used by pregnant women. Females of reproductive potential must be counseled about pregnancy prevention and planning.

6) Steroids (Methylprednisolone / Prednisone)

Description: Adrenal corticosteroid

Mechanism of action:

- Blocks T-cell derived and antigen presenting cell-derived cytokine and cytokine-receptor expression
- Inhibits the expression of IL-1, IL-2, IL-3, and IL-6 as well as TNF-a, IFN-γ.
- Non-specific immunosuppressive effect

Indication: Prophylaxis and/or treatment of rejection in kidney, kidney-pancreas patients

Contraindication: Known hypersensitivity

Dosing: Methylprednisolone is considered as being equivalent to Prednisone on a mg:mg basis at LHSC

Comment:

- If bone density testing is performed and indicates a problem, then bisophosphonate therapy may be considered in addition to current therapy.

Corticosteroid Dosing Protocol

Day	Kidney Transplant	Kidney/Pancreas Transplant
Day 0	Solumedrol 250 mg IV Pre-op on call to OR	Solumedrol 250 mg IV Pre-op on call to OR
POD 1	Solumedrol 1 mg/kg (rounded to nearest 5 mg)	Solumedrol 1 mg/kg (rounded to nearest 5 mg)
POD 2	Prednisone 60 mg PO daily	Prednisone 60 mg PO daily
POD 3	Taper by 5 mg daily to baseline of 20 mg OD	Convert to oral Prednisone 1:1 Taper by 10 mg daily to baseline of 5 mg OD
2 weeks	Taper to alternate day therapy by 6 weeks	
6 weeks to 6 months	Maintenance dose of 15 mg alternate days	
6 months to 1 year	Maintenance dose of 12.5 mg alternate days	
>1 year	Aim for 10 mg alternate days	

Note: For diabetic population, consider daily dosing of Prednisone for blood glucose stability and ease of insulin / oral agent dose adjustment.

Steroid Taper - Non-Diabetic (taper is 15 mg daily x 1 week then 10 mg daily x 1 week then 15 every other day)

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1	20 mg	15 mg	20 mg	15 mg	20 mg	15 mg	20 mg
Week 2	10 mg	20 mg	10 mg	20 mg	10 mg	20 mg	10 mg
Week 3	20 mg	5 mg	20 mg	5 mg	20 mg	5 mg	20 mg
Week 4	Nil	20 mg	Nil	20 mg	Nil	20 mg	nil
Week 5	15 mg	Nil	15 mg	Nil	15 mg	Nil	15 mg

6 weeks to 6 months - Continue on 15 mg alternate days
6 months to 1 year - Reduce dose to 12.5 mg alternate days
Beyond 1 year - Remain on 10 mg alternate days

Steroid Taper – Diabetic (same as above but stays on 7.5 mg daily)

Week 1	Start Date	17.5 mg x 7 days
Week 2	Start Date	15 mg x 7 days
Week 3	Start Date	12.5 mg x 7 days
Week 4	Start Date	10 mg x 7 days
Week 5	Start Date	7.5 mg Daily
6 weeks to 6 months	Continue on 7.5 mg daily	
6 months	Reduce dose to 5 mg daily	

7) Steroid Avoidance

- Use in low immunological risk patients (unsensitized, 1st transplant) with
  - Hepatitis B, C
  - Psychiatric/Psychological issues can be considered
  - Young women (Cosmetic/body image concerns)
  - High risk for PTDM
  - Bone Disease
- Need Thymoglobulin or Simulect induction, Calcineurin Inhibitor and Mycophenolate Mofetil (CellCept)
- Target Tacrolimus levels with steroid avoidance

  Month 1: 10-12 ng/ml
  Month 1-3: 8-10 ng/ml
  Month 3-6: 6-8 ng/ml
  >6 months: 5-7ng/ml or patient specific
- Patients need to be informed of greater risk of rejection and IF/TA

Day	Dose/Preparation
Day 0	Solumedrol 250 mg IV Pre-op on call to OR
POD 1	Solumedrol 60 mg IV
POD 2	Solumedrol 40 mg IV
POD 3	Prednisone oral 30 mg
POD 4	Prednisone oral 20 mg
POD 5	Prednisone oral 10 mg
POD 6	Discontinue Prednisone

8) Sirolimus (Rapamune®)

Description: Triene macrolide antibiotic from S. hygroscopicus from Easter Island (Rapa Nui)

Mechanism of Action:

- Binds to FKBP12; complex inhibits target of rapamycin and interleukin-2-drivenT-cell proliferation from the G1 to S phase of the cell cycle

Indication: Prevention of rejection in renal transplant recipients

Contraindication: Hypersensitivity to sirolimus

Adverse Effects:

- Hyperlipidemia, thrombocytopenia, delayed wound healing, mouth ulcers, pneumonitis, interstitial lung disease, lymphocele
- Lipid monitoring required

Administration:

- Sirolimus has a long terminal half-life (approximately 62 hr), enabling once-daily administration.
- To attain therapeutic levels more quickly, a loading dose may be prescribed.
- Monitoring by trough levels but levels should be drawn no sooner than five days after initiation of therapy or a change in dose, due to its prolonged half-life.
- Numerous drug interactions (including cyclosporine)

Conversion of CNI to sirolimus therapy with skin cancer (squamous cell cancer)

- Dose: Loading dose is 5 mg od x 3 then 2 mg od
- Monitoring: Aim for trough levels of 8-10 ng/ml by 1 week
- Patients should be informed that there is up to a 5% chance of rejection.
- Caution should be used in patients with pulmonary disorders. Patients should have 24-hour urine protein <1 g

9) Additional drugs

Drug	Description	Mechanism	Toxicity and Comments
Azathioprine	Prodrug that releases 6-mercaptopurine	Converts 6-mercaptopurine to tissue inhibitor of metalloproteinase, which is converted to thioguanine nucleotides that interfere with DNA synthesis; thioguanine derivatives may inhibit purine synthesis	Leucopenia, bone marrow depression, macrocytosis, liver toxicity (uncommon); blood count monitoring required
Rituximab (non-formulary)	Chimeric monoclonal antibody against membrane-spanning four-domain protein CD20	Binds to CD20 on B cells and mediates B-cell lysis	Infusion reactions, hypersensitivity reactions (uncommon)
Alemtuzumab (non-formulary)	Humanized monoclonal antibody against CD52, a 25-to-29-kD membrane protein	Binds to CD52 on all B and T cells, most monocytes, macrophages, and natural killer cells, causing cell lysis and prolonged depletion	Mild cytokine-release syndrome, neutropenia, anemia, idiosyncratic pancytopenia, autoimmune thrombocytopenia, thyroid disease

References and Resources:

Immunosuppressive therapy for kidney transplant in adults, Technology appraisal guidance [TA481] Published: 11 October 2017, National Institute for Health and Care Excellence, nice.org.uk/guidance/ta481

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