Tacrolimus – pancreas transplant

<table>
<tr><th></th><th colspan="2">Recommendations</th><th>Notes/Evidence</th></tr>
<tr><td>Initiation</td><td colspan="2">Post-operative day 1</td><td>• Initiation of tacrolimus should start before or at the time of transplant, rather than delayed until the onset of graft function (UW Health, Very Low, Conditional)</td></tr>
<tr><td>Dosing (initial)</td><td>Non-African American</td><td>NPO - 1 mg twice daily
PO - 0.025 mg/kg (use ABW) by mouth twice daily, rounded to the nearest capsule size</td><td rowspan="4">• Capsules and suspension may be taken with or without food. Since the presence of food affects the bioavailability of tacrolimus, if taken with food, it should be taken consistently the same way each time. (UW Health, Very Low, Conditional)
• Tacrolimus may be given sublingually in patients unable to adequately absorb enteral formulations or in those unable to take oral. If a patient is being transitioned to tacrolimus sublingual from tacrolimus IR, each dose should be divided by 2 and given sublingually. (UW Health, Very Low, Conditional)
• Use of IV tacrolimus should be considered rare and risky. Only after discussion with an experienced transplant pharmacist and the faculty of record can it be considered for patients unable to adequately absorb enteral formulations[a,b]. Conversion from IV to oral tacrolimus is recommended as soon as enteral therapy can be tolerated to minimize risk of anaphylactic reactions that occur with injectables containing castor oil derivatives (UW Health, Very Low, Conditional). Transplant Pharmacist should be consulted to assist in dosing and monitoring therapeutic levels
• LCP-Tacrolimus (Envarsus®) may be utilized in patients with documented intolerable adverse effects with tacrolimus IR or who are unable to obtain a therapeutic drug concentration with the IR formulation. If a patient is being transitioned to LCP-tacrolimus from tacrolimus IR, the total daily dose should be multiplied by 0.8, then rounded to the nearest capsule size. Astagraf, Envarsus, and Prograf are not interchangeable (UW Health, Very Low, Conditional)</td></tr>
<tr><td></td><td>African American</td><td>NPO - 2 mg twice daily
PO - 0.05 mg/kg (use ABW) by mouth twice daily, rounded to the nearest capsule size</td></tr>
<tr><td>Drug-drug Interactions (not an all-inclusive list)</td><td colspan="2">Increases tacrolimus concentration
Check Lexicomp for dose adjustments
<u>Adjust tacrolimus dose empirically:</u>
• Fluconazole
• Posaconazole
• Voriconazole
• Ritonavir
• Letermovir
<u>Monitor tacrolimus levels and adjust as needed:</u>
• Clarithromycin
• Erythromycin</td><td>Decreases tacrolimus concentration
Check Lexicomp for dose adjustments
<u>Monitor tacrolimus levels and adjust as needed:</u>
• Rifampin
• Phenytoin
• Carbamazepine
• Phenobarbital
• Octreotide</td></tr>
<tr><td>Target levels

Dose Adjustments

Labs</td><td colspan="2">Concurrent use of mycophenolate +/- prednisone

Tacrolimus goals may differ if patient is not on mycophenolate +/- prednisone regimen. Goal level should be discussed with provider.

<table>
<tr><th></th><th colspan="2">Target TAC Level</th></tr>
<tr><th></th><th>SPK*</th><th>PTA/PAK</th></tr>
<tr><td>0-3 months:</td><td>8-10 ng/mL</td><td>9-11 ng/mL</td></tr>
<tr><td>3-12 months:</td><td>8-10 ng/mL</td><td>9-11 ng/mL</td></tr>
<tr><td>1-3 years:</td><td>6-8 ng/mL</td><td>7-9 ng/mL</td></tr>
<tr><td>>3 years:</td><td colspan="2">Per provider discretion</td></tr>
</table>
*Follow PTA/PAK goals if secondary SPK or MFI ≥ 100
<table>
<tr><th>Below/Above Target</th><th></th></tr>
<tr><td><u>≥</u>50%*</td><td>Adjust dose by 25-50%</td></tr>
<tr><td><50%</td><td>Adjust dose by 25%</td></tr>
</table>
*Holding doses may be necessary</td><td><u>Laboratory Monitoring:</u>
Tacrolimus (trough), potassium, and creatinine
Inpatient: Daily
Post-Discharge:
<table>
<tr><th>Day</th><th>Frequency</th></tr>
<tr><td>0-60</td><td>Not less than twice weekly</td></tr>
<tr><td>60-90</td><td>Not less than once weekly</td></tr>
<tr><td>91-120</td><td>Not less than twice monthly</td></tr>
<tr><td>120-360</td><td>Not less than once monthly</td></tr>
</table>
As Needed:
• Change in medication formulation, patient status, or creatinine increase <u>≥</u>0.3 mg/dL above baseline
• 3 to 7 days (ideally 4 days) following dose adjustment</td></tr>
</table>

[a]Scott LJ, McKeage K, Keam SJ, Plosker GL. Tacrolimus a further update of its use in management of organ transplantation. *Drugs*. 2003;63(12):1247-1297.
[b]Prograf (tacrolimus) capsules/injection. Package insert. Astellas Pharma US, Inc; 2012.

Adverse effects	Acute kidney injury	• Assess tacrolimus trough level for correlation with elevated creatinine • If all other causes are ruled out and an elevated level is found, discuss with physician the appropriateness of dose reduction • Consult transplant physician regarding further work up elevated creatinine
	Neurological symptoms (tremor, headache)	• Assess tacrolimus trough level for correlation with tremors or headache • If trough level is above goal, adjust tacrolimus dose and follow up with patient • If trough level within target range, no dose adjustment is recommended, follow-up with patient in 1 week to assess continued symptoms and trend severity • If adverse effects are persistent, not improving, or interfering with daily activities and there is no other known cause: o Consult the transplant physician to consider splitting IR tacrolimus to three times daily, converting the patient to LCP-tacrolimus, belatacept, or cyclosporine, or refer to primary care provider for supportive therapy, such as addition of low dose beta blocker (propranolol)
	Post-transplant diabetes mellitus (PTDM) *Diagnosis (2 of the following)* • Sx of DM + casual PG concentrations ≥200 mg/dL • FPG ≥126 mg/dL • 2-hr PG ≥200 mg/dL during an oral glucose tolerance test • Hba1c > 7.0% for more than 2 months	• Diagnosis of Post-transplant diabetes mellitus (PTDM) is defined by the World Health Organization (WHO) and American Diabetes Association (ADA) that develops for the first time after transplantation • Consult transplant physician regarding further work up of hyperglycemia • Consult transplant physician and consider converting the patient to cyclosporine, reassessment of steroid dosing, conversion to LCP-tacrolimus or belatacept with lowered tacrolimus goals

Cyclosporine – pancreas transplant

<table>
<tr><th></th><th colspan="2">Recommendations</th><th>Notes/Evidence</th></tr>
<tr><td>Initiation</td><td colspan="2">Post-operative day 1</td><td>• The initiation of cyclosporine should start before or at the time of transplantation, rather than delayed until the onset of graft function (UW Health, Very Low, Conditional)
• Tacrolimus is the preferred therapy in pancreas transplant (UW Health, Very Low, Conditional)
• If cyclosporine was necessary, cyclosporine modified should be used to prevent variability in absorption. Sandimmune and other non-modified products should not be used in the pancreas transplant population (UW Health, Very Low, Conditional)</td></tr>
<tr><td rowspan="2">Dosing (initial)</td><td>Decreased sensitivity (African-American, >80kg)</td><td>Fixed dose 150 mg by mouth twice daily</td><td rowspan="3">• Neoral/Gengraf (cyclosporine modified) and Sandimmune (cyclosporine non-modified) are not bioequivalent and cannot be used interchangeably (UW Health, Very Low, Conditional)
• Cyclosporine modified is preferred over cyclosporine non-modified (UW Health, Very Low, Conditional)
• Capsules and suspension may be taken with or without food. However, since the presence of food affects the bioavailability of cyclosporine, if taken with food, it should be taken consistently the same way each time. (UW Health, Very Low, Conditional)</td></tr>
<tr><td>Increased sensitivity (NPO, <80kg)</td><td>Fixed dose 100 mg by mouth twice daily</td></tr>
<tr><td>Drug-Drug Interactions (not an all-inclusive list)</td><td>Increases cyclosporine concentration
Check Lexicomp for dose adjustments
<u>Adjust cyclosporine dose empirically:</u>
• Fluconazole
• Posaconazole
• Voriconazole
• Ritonavir
• Letermovir
<u>Monitor cyclosporine levels and adjust as needed:</u>
• Clarithromycin
• Erythromycin</td><td>Decreases cyclosporine concentration
Check Lexicomp for dose adjustments
<u>Monitor cyclosporine levels and adjust as needed:</u>
• Rifampin
• Phenytoin
• Carbamazepine
• Phenobarbital</td></tr>
<tr><td>Target levels

Dose Adjustments

Labs</td><td>
<table>
<tr><th></th><th>Goal CSA Level</th></tr>
<tr><td>0-3 months:</td><td>200-300 ng/mL</td></tr>
<tr><td>3-6 months:</td><td>150-250 ng/mL</td></tr>
<tr><td>>6 months:</td><td>100-200 ng/mL</td></tr>
</table>
<table>
<tr><th>Below/Above Target</th><th></th></tr>
<tr><td><u>≥</u>50%</td><td>Adjust dose 25% to 50%</td></tr>
<tr><td><u>≤</u>50%</td><td>Adjust dose by 25%</td></tr>
</table>
*Holding doses may be necessary
</td><td><u>Laboratory Monitoring:</u>
Cyclosporine (trough), potassium, and creatinine
Inpatient: Daily
Post-Discharge:
<table>
<tr><th>Day</th><th>Frequency</th></tr>
<tr><td>0-60</td><td>Not less than twice weekly</td></tr>
<tr><td>60-90</td><td>Not less than once weekly</td></tr>
<tr><td>91-180</td><td>Not less than twice monthly</td></tr>
<tr><td>181-240</td><td>Not less than once monthly</td></tr>
</table>
As Needed:
• Change in medication formulation, patient status, or creatinine increase <u>≥</u>0.3 mg/dL above baseline
• 3 to 7 days (ideally 4 days) following dose adjustment</td></tr>
</table>

Adverse effects	Acute kidney injury	• Assess cyclosporine trough level for correlation with elevated creatinine • If trough level is above goal and creatinine has increased ≥ 0.3 mg/dL above baseline: o Decrease cyclosporine dose if trough is <50 ng/mL above goal o Hold cyclosporine if trough ≥50 ng/mL above goal and consider increasing current prednisone dose • Consult transplant physician regarding further work up elevated creatinine
	Neurological symptoms (tremor, headache)	• Assess cyclosporine trough level for correlation with tremors or headache • If trough level is above goal, adjust cyclosporine dose and follow up with patient • If trough level within target range, no dose adjustment is recommended, follow-up with patient in 1 week to assess continued symptoms and trend severity • If adverse effects are intolerable or interacting with daily activities and there is no other known cause of symptom: o Consult the transplant physician to consider converting the patient to LCP-tacrolimus, belatacept, or refer to primary care provider for supportive therapy, such as addition of low dose beta blocker (propranolol)
	Post-transplant diabetes mellitus (PTDM) *Diagnosis (2 of the following)* • Sx of DM + casual PG concentrations ≥200 mg/dL • FPG ≥126 mg/dL • 2-hr PG ≥200 mg/dL during an oral glucose tolerance test • Hba1c > 7.0% for more than 2 months	• No cyclosporine dose adjustment is recommended • Consider consulting diabetes management & nutrition services • Diagnosis of Post-transplant diabetes mellitus (PTDM) is defined by the World Health Organization (WHO) and American Diabetes Association (ADA) that develops for the first time after transplantation • Consult transplant physician regarding further work up of hyperglycemia o Consult transplant physician and consider reassessment of steroid dosing, or conversion to belatacept with lowered tacrolimus goals

Mycophenolate – pancreas transplant

<table>
<tr><th></th><th>Recommendation</th><th>Notes/Evidence</th></tr>
<tr><td>Initiation</td><td>Post-operative day 1</td><td rowspan="3">• Full dose mycophenolic acid is the preferred anti-proliferative medication used for PTA, PAK, and SPK transplant patients (UW Health, Very Low, Conditional)
• IV mycophenolate mofetil is administered for the first 4 doses after transplant and may also be indicated if the patient has an acute condition that affects gastrointestinal absorption (i.e., GI bleed or obstruction, malabsorption syndromes, severe diarrhea or severe vomiting) (UW Health, Very Low, Conditional)
• Mycophenolate mofetil suspension is utilized for patients receiving medications via nasogastric or orogastric tube</td></tr>
<tr><td>Dosing (initial)</td><td>
<table>
<tr><td rowspan="2">Mycophenolate mofetil</td><td>1000 mg IV x 1 dose</td><td>POD0</td></tr>
<tr><td>1000 mg IV twice daily x 4 doses</td><td>POD1-2</td></tr>
<tr><td>Mycophenolate sodium</td><td>720 mg PO twice daily</td><td>POD3</td></tr>
<tr><td colspan="3">*Note: if sum MFI 1000-4000 or patient is African American, consider 720 mg TID on POD3 and discharge</td></tr>
</table>
</td></tr>
<tr><td>Drug-drug interactions (not an all-inclusive list)</td><td>Decreases mycophenolate concentration
Check Lexicomp for dose adjustments
• Cyclosporine
• Bile acid sequestrants

Mycophenolate decreases concentration of estrogen derivatives. Women of childbearing potential who are receiving mycophenolate mofetil should consider using an alternative and/or additional form of contraception.</td></tr>
<tr><td>Target levels

Labs</td><td>
<table>
<tr><th></th><th>Goal MPA Trough[c]</th></tr>
<tr><td>CsA based regimens:</td><td>1.3-2.8 mg/L</td></tr>
<tr><td>TAC based regimens:</td><td>1.9-2.8 mg/L</td></tr>
</table>
</td><td><u>Laboratory Monitoring:</u>
• Lab monitoring of MPA levels is not recommended to assess for toxicity or efficacy
• If levels are requested, they are only appropriate for mycophenolate mofetil and should be drawn as a trough</td><td>• MPA AUC is a better predictor of clinical events than MPA trough. Trough levels are poorly correlated with AUC and are not recommended (UW Health, Very Low, Conditional)</td></tr>
<tr><td rowspan="2">Adverse effects</td><td>Diarrhea

If a patient has ≥50% increase in their frequency of daily bowel movements for ≥ 5-7 days
• 0-3 months post-transplant:
o C. difficile, C. difficile toxin B PCR
o CMV PCR
• ≥3 months post-transplant:
o CMV PCR
o Complete blood count
o Clostridium difficile toxin B PCR
o Cryptosporidium
o Giardia PCR
o Norovirus PCR
o Rotavirus AG
o Stool culture, with E. Coli (Shiga) toxin
o Stool O&P (parasitology, isospora, cyclospora, pinworm)
o Consider colonoscopy if diarrhea persists and all stool studies are negative</td><td colspan="2">• If diarrhea work-up is negative for an infectious cause of diarrhea and it is affecting activities of daily living or the patient is having limited and/or decreased oral intake:
o Decrease mycophenolate by 25% and increase dosing frequency (ex. 720 mg BID → 360 mg TID)
▪ If fails, decrease mycophenolate by 50%
o Follow up with patient in 1 week to assess continued symptoms and trend severity
o If dose is decreased to 180 mg twice daily (MYF) or 250 mg twice daily (MMF) consult provider to determine if other immunosuppression needs to be adjusted
o Consider adding the following:
▪ Add loperamide (Imodium®) 2 mg as needed after each loose stool (max dose: 16 mg daily)
▪ Diphenoxylate/atropine (Lomotil®) 5 mg four times daily as needed (max dose: 20 mg/day)
▪ Psyllium fiber (Metamucil®) 3.4 g daily as needed</td></tr>
<tr><td>Leukopenia</td><td colspan="2">• Consult transplant physician regarding further work up of leukopenia and to determine if immunosuppression needs to be adjusted</td></tr>
</table>

	Heartburn/nausea	• Counsel patient on taking MYF or MMF with food if not already doing so • Convert from MMF to MYF if only upper GI complaints (heartburn, nausea) • Add calcium carbonate as needed, or the addition of an H2RA or PPI if not already on • If symptoms continue following one week of daily thearpy, increase H2RA or PPI dose to twice daily, reassess in 1 week • If symptoms persist for ≥1 week, consider EGD to rule out infection vs. ulceration

[c]Gaston RS, Kaplan B, Shah T, et al. Fixed- or controlled-dose mycophenolate mofetil with standard or reduced-dose calcineurin inhibitors: the opticept trial. *Am J Transplant*. 2009;9(7):1607-19.

Prednisone – pancreas transplant

<table>
<tr><th></th><th>Recommendations</th><th>Notes/Evidence</th></tr>
<tr><td>Initiation</td><td>Post-operative day 4 following dexamethasone taper</td><td>• Prednisone 30 mg once daily will be started on POD 4 following dexamethasone taper and may be continued on discharge</td></tr>
<tr><td>Dosing (initial)</td><td>Standard steroid taper
• Factors that may influence the duration of prednisone taper:
o Current and historical CNI levels
o Sensitization status
o Current MPA dose
o Episodes of rejection
<table>
<tr><td rowspan="2">Dexamethasone</td><td>100 mg</td><td>POD0</td></tr>
<tr><td>50 mg</td><td>POD1</td></tr>
<tr><td rowspan="2">Dexamethasone or Prednisone</td><td>18 mg (dex) or 90 mg (pred)</td><td>POD2</td></tr>
<tr><td>12 mg (dex) or 60 mg (pred)</td><td>POD3</td></tr>
<tr><td rowspan="2">Prednisone</td><td>30 mg</td><td>POD4</td></tr>
<tr><td colspan="2">Discharge on 30 mg and after 2 week follow up, decrease dose by 5 mg each week to a target dose of 10 mg daily</td></tr>
</table>
Rapid steroid taper
<table>
<tr><td rowspan="2">Dexamethasone</td><td>100 mg</td><td>POD0</td></tr>
<tr><td>50 mg</td><td>POD1</td></tr>
<tr><td rowspan="2">Dexamethasone or Prednisone</td><td>18 mg (dex) or 90 mg (pred)</td><td>POD2</td></tr>
<tr><td>12 mg (dex) or 60 mg (pred)</td><td>POD3</td></tr>
<tr><td rowspan="4">Prednisone</td><td>30 mg</td><td>POD4</td></tr>
<tr><td>20 mg</td><td>POD5</td></tr>
<tr><td>10 mg</td><td>POD6</td></tr>
<tr><td colspan="2">Discharge on 10 mg daily and decrease to 5 mg daily after 2 weeks if tacrolimus is therapeutic</td></tr>
</table>
Early steroid withdrawal
<table>
<tr><td rowspan="2">Dexamethasone</td><td>100 mg</td><td>POD0</td></tr>
<tr><td>50 mg</td><td>POD1</td></tr>
<tr><td rowspan="2">Dexamethasone or Prednisone</td><td>18 mg (dex) or 90 mg (pred)</td><td>POD2</td></tr>
<tr><td>12 mg (dex) or 60 mg (pred)</td><td>POD3</td></tr>
<tr><td rowspan="2">Prednisone</td><td>30 mg</td><td>POD4</td></tr>
<tr><td colspan="2">Steroid withdrawal on POD5</td></tr>
</table></td><td>• Steroid withdrawal can be considered for patients who receive alemtuzumab for induction (UW Health, Very Low, Conditional)
• Rapid steroid taper can be considered for patients who receive alemtuzumab or thymoglobulin for induction (UW Health, Very Low, Conditional)
• Prednisone doses should be split to twice daily dosing for patients requiring glucose control (UW Health, Very Low, Conditional)</td></tr>
<tr><td>Labs</td><td colspan="2">Laboratory Monitoring: Glucose, bone mineral density</td></tr>
<tr><td rowspan="3">Adverse effects</td><td>Hyperglycemia</td><td>• Prednisone doses should be split to twice daily dosing for patients with hyperglycemia</td></tr>
<tr><td>Heartburn/reflux</td><td>• Start proton pump inhibitor (PPI) at time of transplant. Should be continued for at least 3 months after transplant
• If a patient complains of heartburn on daily dosing of the PPI, frequency may be increased to twice daily (pending renal function)
• Discontinue PPI in patients with no history of heartburn/gastroesophageal reflux disease (GERD) prior to transplant if prednisone is discontinued</td></tr>
<tr><td>Osteoporosis</td><td>• Recommend calcium 1200 mg daily (based on elemental calcium dosing)
• Recommend vitamin D 2000 units daily
• For patients that are on an early steroid withdrawal maintenance immunosuppression regimen, calcium and vitamin D supplementation are not required</td></tr>
</table>