

## Tacrolimus – liver transplant

|   |  | Recommendations                   |   | Notes/Evidence  |                     |           |      |              |       |                      |        |                             |         |                            |
|---|--|-----------------------------------|---|---|---------------------|-----------|------|--------------|-------|----------------------|--------|-----------------------------|---------|----------------------------|
| Initiation  | Post-operative day 1   |                                   |   | <ul style="list-style-type: none"> <li>Initiation of tacrolimus should on post-operative day 1 after transplant (UW Health, Very Low, Conditional)</li> </ul>   |                     |           |      |              |       |                      |        |                             |         |                            |
| Dosing (initial)  | Standard dosing  |                                   | Fixed dose 2 mg by mouth twice daily  | <ul style="list-style-type: none"> <li>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)</li> </ul>   |                     |           |      |              |       |                      |        |                             |         |                            |
|   | Increased sensitivity (on CYP3A4 inhibitor - see list below)   |                                   | Fixed dose 1 mg by mouth twice daily  |   |                     |           |      |              |       |                      |        |                             |         |                            |
| Drug-drug Interactions (not an all-inclusive list)  | <b>Increases</b> tacrolimus concentration<br><b>*Check Lexicomp for dose adjustments*</b><br><u>Adjust tacrolimus dose empirically for the following CYP4 inhibitors:</u> <ul style="list-style-type: none"> <li>Fluconazole</li> <li>Posaconazole</li> <li>Voriconazole</li> <li>Ritonavir</li> <li>Letermovir</li> </ul> <u>Monitor tacrolimus levels and adjust as needed:</u> <ul style="list-style-type: none"> <li>Clarithromycin</li> <li>Erythromycin</li> </ul> |                                   | <b>Decreases</b> tacrolimus concentration<br><b>*Check Lexicomp for dose adjustments*</b><br><u>Monitor tacrolimus levels and adjust as needed:</u> <ul style="list-style-type: none"> <li>Rifampin</li> <li>Phenytoin</li> <li>Carbamazepine</li> <li>Phenobarbital</li> </ul> | <ul style="list-style-type: none"> <li>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)</li> <li>Use of IV should be considered rare and risky and only considered in the inpatient setting. Only after discussion with an experienced transplant pharmacist and the faculty of record can it be considered. 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)</li> <li>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 tablet size. Astagraf, Envarsus, and Prograf are not interchangeable (UW Health, Very Low, Conditional)</li> </ul> |                     |           |      |              |       |                      |        |                             |         |                            |
| Target levels   |  | Autoimmune disease and not on MPA | NOT autoimmune OR on MPA  | <b>Laboratory Monitoring:</b><br>Tacrolimus (trough), potassium, and creatinine<br><b>Inpatient:</b> Daily<br><b>Outpatient:</b> <table border="1" data-bbox="850 925 1396 1161"> <thead> <tr> <th>Day after discharge</th> <th>Frequency</th> </tr> </thead> <tbody> <tr> <td>0-30</td> <td>Twice weekly</td> </tr> <tr> <td>31-90</td> <td>Not less than weekly</td> </tr> <tr> <td>91-180</td> <td>Not less than twice monthly</td> </tr> <tr> <td>181-365</td> <td>Not less than once monthly</td> </tr> </tbody> </table> <b>Modify as Needed on a Patient-by-Patient basis:</b> <ul style="list-style-type: none"> <li>Change in medication formulation, patient status, or creatinine increase <math>\geq 0.3</math> mg/dL above baseline</li> <li>3 to 7 days (ideally 4 days) following dose adjustment</li> </ul>   | Day after discharge | Frequency | 0-30 | Twice weekly | 31-90 | Not less than weekly | 91-180 | Not less than twice monthly | 181-365 | Not less than once monthly |
| Day after discharge   | Frequency  |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| 0-30  | Twice weekly   |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| 31-90   | Not less than weekly   |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| 91-180  | Not less than twice monthly  |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| 181-365   | Not less than once monthly   |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| Dose Adjustments  | 0-3 months:  | 8-10 ng/mL                        | 5-7 ng/mL   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| Labs  | 3-6 months:  | 8-10 ng/mL                        | 5-7ng/mL  |   |                     |           |      |              |       |                      |        |                             |         |                            |
|   | 6-12 months:   | 6-8 ng/mL                         | 3-5 ng/mL   |   |                     |           |      |              |       |                      |        |                             |         |                            |
|   | >12 months:  | 4-6 ng/mL                         | 2-5 ng/mL   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| <b>*Above trough goals are general guidance, and immunosuppression should be tailored to patient's immunologic risk and tolerance of medications*</b> |  |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
|   | Below/Above Target   |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
|   | $\geq 50\%$  | Adjust dose by 25-50%*            |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
|   | $< 50\%$   | Adjust dose by 25%                |   |   |                     |           |      |              |       |                      |        |                             |         |                            |
| *Holding doses may be necessary   |  |                                   |   |   |                     |           |      |              |       |                      |        |                             |         |                            |

|                 |   |   |
|-----------------|---|---|
| Adverse effects | Acute kidney injury   | <ul style="list-style-type: none"> <li>Assess tacrolimus trough level for correlation with elevated creatinine</li> <li>If trough level is above goal and creatinine has increased <math>\geq 0.3</math> mg/dL above baseline:                             <ul style="list-style-type: none"> <li>Decrease tacrolimus dose if trough is <math>&lt;4</math> ng/mL above goal</li> <li>Hold tacrolimus if trough <math>\geq 5</math> ng/mL above goal and consider increasing current prednisone dose</li> </ul> </li> <li>Consult transplant physician regarding further work up elevated creatinine</li> </ul>  |
|                 | Neurological symptoms (tremor, headache)  | <ul style="list-style-type: none"> <li>Assess tacrolimus trough level for correlation with tremors or headache</li> <li>If trough level is above goal, adjust tacrolimus dose and follow up with patient</li> <li>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</li> <li>If adverse effects are persistent, not improving, or interfering with daily activities and there is no other known cause:                             <ul style="list-style-type: none"> <li>Consult the transplant physician to consider splitting IR tacrolimus to three times daily or converting the patient to LCP-tacrolimus or cyclosporine</li> <li>Addition of a low dose propranolol may also be considered if heart rate <math>&gt;60</math> BPM, systolic blood pressure <math>&gt;120</math> mmHg, and patient is not already on a beta blocker</li> </ul> </li> </ul> |
|                 | New onset diabetes after transplantation (NODAT)<br><br><i>Diagnosis (2 of the following)</i> <ul style="list-style-type: none"> <li>Sx of DM + casual PG concentrations <math>\geq 200</math> mg/dL</li> <li>FPG <math>\geq 126</math> mg/dL</li> <li>2-hr PG <math>\geq 200</math> mg/dL during an oral glucose tolerance test</li> <li>Hba1c <math>&gt; 7.0\%</math> for more than 2 months</li> </ul> | <ul style="list-style-type: none"> <li>No tacrolimus dose adjustment is recommended</li> <li>Consult diabetes management &amp; nutrition services</li> <li>Diagnosis of new onset diabetes after transplant (NODAT) is defined by the World Health Organization (WHO) and American Diabetes Association (ADA) that develops for the first time after transplantation</li> <li>Continue planned discontinuation of glucocorticoids by 2 months</li> <li>If there is no improvement in glucose control 6 months after transplant (NODAT requiring insulin OR A1c <math>&gt;7\%</math> with glucose lowering agent):                             <ul style="list-style-type: none"> <li>Consult transplant physician and consider reassessment of steroid dosing or conversion to LCP-tacrolimus</li> </ul> </li> </ul>  |

## Cyclosporine – liver transplant

|   |  | Recommendations                   |   | Notes/Evidence  |     |           |      |              |       |                      |        |                             |         |                            |
|---|--|-----------------------------------|---|---|-----|-----------|------|--------------|-------|----------------------|--------|-----------------------------|---------|----------------------------|
| Initiation  | Post-operative day 1   |                                   |   | <ul style="list-style-type: none"> <li>The initiation of cyclosporine should start post-operative day 1 after transplant (UW Health, Very Low, Conditional)</li> </ul>  |     |           |      |              |       |                      |        |                             |         |                            |
| Dosing (initial)  | Standard dosing  |                                   | Fixed dose 150 mg by mouth twice daily  | <ul style="list-style-type: none"> <li>Neoral/Gengraf (cyclosporine modified) and Sandimmune (cyclosporine non-modified) are not bioequivalent and cannot be used interchangeably (UW Health, Very Low, Conditional)</li> <li>Cyclosporine modified is preferred over cyclosporine non-modified (UW Health, Very Low, Conditional)</li> <li>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)</li> </ul>   |     |           |      |              |       |                      |        |                             |         |                            |
|   | Increased sensitivity (on CYP3A4 inhibitor - see list below)   |                                   | Fixed dose 100 mg by mouth twice daily  |   |     |           |      |              |       |                      |        |                             |         |                            |
| Drug-Drug Interactions (not an all-inclusive list)  | <b>Increases</b> cyclosporine concentration<br><b>*Check Lexicomp for dose adjustments*</b><br><u>Adjust cyclosporine dose empirically for the following CYP4 inhibitors:</u> <ul style="list-style-type: none"> <li>Fluconazole</li> <li>Posaconazole</li> <li>Voriconazole</li> <li>Ritonavir</li> <li>Letermovir</li> </ul> <u>Monitor cyclosporine levels and adjust as needed:</u> <ul style="list-style-type: none"> <li>Clarithromycin</li> <li>Erythromycin</li> </ul> |                                   | <b>Decreases</b> cyclosporine concentration<br><b>*Check Lexicomp for dose adjustments*</b><br><u>Monitor cyclosporine levels and adjust as needed:</u> <ul style="list-style-type: none"> <li>Rifampin</li> <li>Phenytoin</li> <li>Carbamazepine</li> <li>Phenobarbital</li> </ul> |   |     |           |      |              |       |                      |        |                             |         |                            |
| Target levels   |  | Autoimmune disease and not on MPA | NOT autoimmune OR on MPA  | <b>Laboratory Monitoring:</b><br>Cyclosporine (trough), potassium, and creatinine<br><b>Inpatient:</b> Daily<br><b>Post-Discharge:</b> <table border="1"> <thead> <tr> <th>Day</th> <th>Frequency</th> </tr> </thead> <tbody> <tr> <td>0-30</td> <td>Twice weekly</td> </tr> <tr> <td>31-90</td> <td>Not less than weekly</td> </tr> <tr> <td>91-180</td> <td>Not less than twice monthly</td> </tr> <tr> <td>181-365</td> <td>Not less than once monthly</td> </tr> </tbody> </table> <b>Modify as Needed on a Patient-by-Patient basis:</b> <ul style="list-style-type: none"> <li>Change in medication formulation, patient status, or creatinine increase <math>\geq 0.3</math> mg/dL above baseline</li> <li>3 to 7 days (ideally 4 days) following dose adjustment</li> </ul> | Day | Frequency | 0-30 | Twice weekly | 31-90 | Not less than weekly | 91-180 | Not less than twice monthly | 181-365 | Not less than once monthly |
| Day   | Frequency  |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
| 0-30  | Twice weekly   |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
| 31-90   | Not less than weekly   |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
| 91-180  | Not less than twice monthly  |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
| 181-365   | Not less than once monthly   |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
| Dose Adjustments  | 0-3 mo:  | 150-200 ng/mL                     | 125-175 ng/mL   |   |     |           |      |              |       |                      |        |                             |         |                            |
| Labs  | 3-6 mo:  | 125-150 ng/mL                     | 125-150 ng/mL   |   |     |           |      |              |       |                      |        |                             |         |                            |
|   | 6-12 mo:   | 100-125 ng/mL                     | 75-100 ng/mL  |   |     |           |      |              |       |                      |        |                             |         |                            |
|   | >12 mo:  | 100 ng/mL                         | 50-75 ng/mL   |   |     |           |      |              |       |                      |        |                             |         |                            |
| <b>*Above trough goals are general guidance, and immunosuppression should be tailored to patient's immunologic risk and tolerance of medications*</b> |  |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
|   | Below/Above Target   |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |
|   | $\geq 50\%$  | Adjust dose 25% to 50%            |   |   |     |           |      |              |       |                      |        |                             |         |                            |
|   | $\leq 50\%$  | Adjust dose by 25%                |   |   |     |           |      |              |       |                      |        |                             |         |                            |
| *Holding doses may be necessary   |  |                                   |   |   |     |           |      |              |       |                      |        |                             |         |                            |

|                 |   |   |
|-----------------|---|---|
| Adverse effects | Acute kidney injury   | <ul style="list-style-type: none"> <li>• Assess cyclosporine trough level for correlation with elevated creatinine</li> <li>• If trough level is above goal and creatinine has increased <math>\geq 0.3</math> mg/dL above baseline:                             <ul style="list-style-type: none"> <li>○ Decrease cyclosporine dose if trough is <math>&lt; 50</math> ng/mL above goal</li> <li>○ Hold cyclosporine if trough <math>\geq 50</math> ng/mL above goal and consider increasing current prednisone dose</li> </ul> </li> <li>• Consult transplant physician regarding further work up elevated creatinine</li> </ul>   |
|                 | Neurological symptoms (tremor, headache)  | <ul style="list-style-type: none"> <li>• Assess cyclosporine trough level for correlation with tremors or headache</li> <li>• If trough level is above goal, adjust cyclosporine dose and follow up with patient</li> <li>• 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</li> <li>• If adverse effects are intolerable or interacting with daily activities and there is no other known cause of symptom:                             <ul style="list-style-type: none"> <li>○ Consult the transplant physician to consider converting the patient to LCP-tacrolimus</li> <li>○ Addition of a low dose propranolol may also be considered if heart rate <math>&gt; 60</math> BPM, systolic blood pressure <math>&gt; 120</math> mmHg, and patient is not already on a beta blocker</li> </ul> </li> </ul> |
|                 | New onset diabetes after transplantation (NODAT)<br><br><i>Diagnosis (2 of the following)</i> <ul style="list-style-type: none"> <li>• Sx of DM + casual PG concentrations <math>\geq 200</math> mg/dL</li> <li>• FPG <math>\geq 126</math> mg/dL</li> <li>• 2-hr PG <math>\geq 200</math> mg/dL during an oral glucose tolerance test</li> <li>• Hba1c <math>&gt; 7.0\%</math> for more than 2 months</li> </ul> | <ul style="list-style-type: none"> <li>• No cyclosporine dose adjustment is recommended</li> <li>• Consult diabetes management &amp; nutrition services</li> <li>• Diagnosis of new onset diabetes after transplant (NODAT) is defined by the World Health Organization (WHO) and American Diabetes Association (ADA) that develops for the first time after transplantation</li> <li>• Continue planned discontinuation of glucocorticoids by 60 days</li> <li>• If there is no improvement in glucose control 6 months after transplant (NODAT requiring insulin OR A1c <math>&gt; 7\%</math> with glucose lowering agent):                             <ul style="list-style-type: none"> <li>• Consult transplant physician and consider reassessment of steroid dosing or conversion to other immunosuppressant</li> </ul> </li> </ul>   |



## Mycophenolate – liver transplant

|  | Recommendation  |   |        | Notes/Evidence  |
|--|---|---|--------|---|
| Initiation   | Post-operative day 0  |   |        | <ul style="list-style-type: none"> <li>• Full dose mycophenolic acid is the preferred anti-proliferative medication used for liver transplant patients (UW Health, Very Low, Conditional)</li> <li>• IV mycophenolate mofetil is 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)</li> <li>• Mycophenolate mofetil suspension is utilized for patients receiving medications via nasogastric or orogastric tube</li> </ul>  |
| Dosing (initial)                                   | Mycophenolate mofetil   | 1000 mg IV x 1 dose   | POD0   |   |
|  | Mycophenolate sodium  | 1000 mg IV twice daily x 4 doses  | POD1-2 |   |
|  |   | 720 mg PO twice daily and after   | POD3   |   |
| Drug-drug interactions (not an all-inclusive list) | <p>Medications that <b>decrease</b> mycophenolate concentration</p> <ul style="list-style-type: none"> <li>• Cyclosporine</li> <li>• Bile acid sequestrants</li> </ul> <p>Mycophenolate <b>decreases</b> concentration of estrogen derivatives. Women of childbearing potential who are receiving mycophenolate mofetil should consider using an alternative and/or additional form of contraception.</p> <p><b>*Check Lexicomp for dose adjustments*</b></p>   |   |        |   |
| Target levels                                      |   | <b>Goal MPA Trough</b>  |        | <ul style="list-style-type: none"> <li>• 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)</li> <li>• Levels may be utilized for assessing safety; not recommended to assess efficacy</li> </ul>  |
| Labs   | <b>CsA or TAC based regimens</b>  | 1.0-3.5 mg/L  |        |   |
|  | <p><u>Laboratory Monitoring:</u></p> <ul style="list-style-type: none"> <li>• Lab monitoring of MPA levels is not recommended to assess for toxicity or efficacy</li> <li>• If levels are requested, they are only appropriate for mycophenolate mofetil and should be drawn as a trough</li> </ul>   |   |        |   |
| Adverse effects                                    | <p><b>Diarrhea</b></p> <p>If a patient has <math>\geq 50\%</math> increase in their frequency of daily bowel movements for <math>\geq 5-7</math> days</p> <ul style="list-style-type: none"> <li>• 0-3 months post-transplant: <ul style="list-style-type: none"> <li>○ C. difficile, C. difficile toxin B PCR</li> <li>○ CMV PCR</li> </ul> </li> <li>• <math>\geq 3</math> months post-transplant: <ul style="list-style-type: none"> <li>○ CMV PCR</li> <li>○ Complete blood count</li> <li>○ Clostridium difficile toxin B PCR</li> <li>○ Cryptosporidium</li> <li>○ Giardia PCR</li> <li>○ Norovirus PCR</li> <li>○ Rotavirus AG</li> <li>○ Stool culture, with E. Coli (Shiga) toxin</li> <li>○ Stool O&amp;P (parasitology, isospora, cyclospora, pinworm)</li> <li>○ Consider colonoscopy if diarrhea persists and all stool studies are negative</li> </ul> </li> </ul> <p>*In any patient post-liver transplant with diarrhea in the first 6 months, consider graft-versus-host disease</p> |   |        | <ul style="list-style-type: none"> <li>• 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: <ul style="list-style-type: none"> <li>○ Decrease mycophenolate by 25% and increase dosing frequency (ex. 720 mg BID <math>\rightarrow</math> 360 mg TID) <ul style="list-style-type: none"> <li>▪ If fails, decrease mycophenolate by 50%</li> </ul> </li> <li>○ Follow up with patient in 1 week to assess continued symptoms and trend severity</li> <li>○ 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</li> <li>○ Consider adding the following: <ul style="list-style-type: none"> <li>▪ Add loperamide (Imodium®) 2 mg as needed after each loose stool (max dose: 16 mg daily)</li> <li>▪ Diphenoxylate/atropine (Lomotil®) 5 mg four times daily as needed (max dose: 20 mg/day)</li> <li>▪ Psyllium fiber (Metamucil®) 3.4 g daily as needed</li> </ul> </li> </ul> </li> <li>• If patient is continuing to have symptoms despite lowering immunosuppression, discuss with transplant provider</li> </ul> |
|  |   | <p><b>Leukopenia</b></p> <ul style="list-style-type: none"> <li>• Consult transplant physician regarding further work up leukopenia</li> <li>• Adjust dose based on following recommendations: <ul style="list-style-type: none"> <li>○ WBC 2-4 x 10<sup>9</sup>/L: Could consider decrease in total daily dose by 50%</li> <li>○ WBC &lt;2 x 10<sup>9</sup>/L: Hold doses until leukopenia resolves</li> </ul> </li> </ul> |        |   |

|  |                  |   |
|--|------------------|---|
|  |                  | <ul style="list-style-type: none"><li>• Consider dose modifications or discontinuations of other medications that may cause leukopenia</li><li>• If leukopenia persists despite medication changes, consider graft-versus-host disease</li></ul>  |
|  | Heartburn/nausea | <ul style="list-style-type: none"><li>• Counsel patient on taking MYF or MMF with food if not already doing so</li><li>• Convert from MMF to MYF if only upper GI complaints (heartburn, nausea)</li><li>• Add calcium carbonate as needed, or the addition of an H2RA or PPI if not already on</li><li>• If symptoms continue following 1 week of daily therapy increase H2RA or PPI dose to twice daily, reassess in 1 week</li><li>• If symptoms persist for <math>\geq 1</math> week, consider EGD to rule out infection vs. ulceration</li></ul> |

UWHealth

## Azathioprine – liver transplant

|  | Recommendation   | Notes/Evidence   |
|--|--|--|
| Initiation   | Failure to tolerate mycophenolate  | <ul style="list-style-type: none"> <li>Azathioprine is recommended for use in patients unable to tolerate adverse effects of mycophenolate (UW Health, Very Low, Conditional)</li> </ul>   |
| Dosing (initial)                                   | 1-3 mg/kg by mouth daily rounded to nearest 25 mg dose   | <ul style="list-style-type: none"> <li>Azathioprine is considered to be less effective than MPA in preventing rejection. Prior to initiating azathioprine, consider the total immunosuppression for the patient and timing out from transplant</li> <li>Azathioprine 50 mg tablets should be prescribed as azathioprine 75 and 100 mg tablets are not available as generic and are more expensive</li> </ul> |
| Drug-drug interactions (not an all-inclusive list) | <p><b>Increases</b> azathioprine concentration:<br/> <b>*Check Lexicomp for dose adjustments*</b><br/> <u>Avoid concurrent use:</u></p> <ul style="list-style-type: none"> <li>Febuxostat</li> </ul> <p><u>Adjust azathioprine dose empirically:</u></p> <ul style="list-style-type: none"> <li>Allopurinol</li> </ul>   |  |
| Labs   | <p><u>Laboratory Monitoring:</u></p> <ul style="list-style-type: none"> <li>Monitor CBC with differential and platelets weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dose modifications</li> <li>Monitor LFTs every 3 months while on treatment</li> <li>There is no recommended azathioprine level for monitoring purposes. However, if toxicity is suspected, check thiopurine methyltransferase (TPMT)</li> </ul>   |  |
| Adverse effects                                    | Leukopenia   | <ul style="list-style-type: none"> <li>Consult transplant provider if WBC &lt;3 and consider checking thiopurine methyltransferase (TPMT)</li> </ul>   |
|  | Gastrointestinal<br><br>If a patient has ≥50% increase in their frequency of daily bowel movements for ≥ 5-7 days <ul style="list-style-type: none"> <li>0-3 months post-transplant:               <ul style="list-style-type: none"> <li>C. difficile, C. difficile toxin B PCR</li> <li>CMV PCR</li> </ul> </li> <li>≥3 months post-transplant:               <ul style="list-style-type: none"> <li>CMV PCR</li> <li>Complete blood count</li> <li>Clostridium difficile toxin B PCR</li> <li>Cryptosporidium</li> <li>Giardia PCR</li> <li>Norovirus PCR</li> <li>Rotavirus AG</li> <li>Stool culture, with E. Coli (Shiga) toxin</li> <li>Stool O&amp;P (parasitology, isospora, cyclospora, pinworm)</li> </ul> </li> </ul> Consider colonoscopy if diarrhea persists and all stool studies are negative | <ul style="list-style-type: none"> <li>See diarrhea work-up algorithm</li> </ul>   |
|  | Pancreatitis   | <ul style="list-style-type: none"> <li>Consult transplant provider if suspected based on patient symptoms</li> </ul>   |

## Sirolimus/everolimus – liver transplant

|   | Recommendations  |  | Notes/Evidence   |
|---|--|--|--|
| Initiation  | For use in patients with: <ul style="list-style-type: none"> <li>• CNI toxicity</li> <li>• Skin cancer</li> <li>• Recurrent hepatocellular carcinoma</li> <li>• Renal dysfunction</li> </ul> Quadruple therapy   |  | <ul style="list-style-type: none"> <li>• Sirolimus/everolimus may impair or delay wound healing, and should be used with caution in the peri-surgical period (UW Health, Very Low, Conditional)</li> <li>• Sirolimus should not be used within 30 days of liver transplant due to risk of hepatic artery thrombosis (UW Health, Very Low, Conditional)</li> <li>• May be indicated for use in patients with recurrent skin cancers as a replacement for azathioprine, MPA, or CNIs (UW Health, Very Low, Conditional)</li> </ul> |
| Dosing (initial)  | Sirolimus  | 2 mg by mouth once daily   |  |
|   | Everolimus   | 0.75 mg by mouth twice daily   |  |
| Drug-drug interactions (not an all-inclusive list)  | <b>Increase</b> mTOR concentration (not an all-inclusive list):<br><b>*Check Lexicomp for dose adjustments*</b><br><u>Avoid concurrent use:</u> <ul style="list-style-type: none"> <li>• Posaconazole</li> <li>• Voriconazole</li> <li>• Ritonavir</li> </ul> <u>Monitor mTOR levels and adjust as needed:</u> <ul style="list-style-type: none"> <li>• Fluconazole</li> <li>• Ritonavir</li> <li>• Letemovir</li> <li>• Clarithromycin</li> <li>• Erythromycin</li> </ul> | <b>Decrease</b> mTOR concentration (not an all-inclusive list)<br><b>*Check Lexicomp for dose adjustments*</b><br><u>Monitor mTOR levels and adjust as needed:</u> <ul style="list-style-type: none"> <li>• Rifampin</li> <li>• Phenytoin</li> <li>• Carbamazepine</li> <li>• Phenobarbital</li> </ul> |  |
| Target levels   |  | Goal Trough Levels (Siro/Evr+FK)   | Goal Trough Levels (Siro/Evr+MPA)  |
| Dose Adjustments  | 0-3 mo:  | Siro/Evr: 4-7 ng/mL; FK: 5-7 ng/mL   | Siro/Evr: 8-10 ng/mL   |
|   | 3-6 mo:  | Siro/Evr: 4-7 ng/mL; FK: 5-7 ng/mL   | Siro/Evr: 8-10 ng/mL   |
|   | 6-12 mo:   | Siro/Evr: 3-5 ng/mL; FK: 3-5 ng/mL   | Siro/Evr: 5-8 ng/mL  |
| Labs  | >12 mo:  | Siro/Evr: 3-5 ng/mL; FK: 3-5 ng/mL   | Siro/Evr: 5-8 ng/mL  |
| <p><b>*Above trough goals are general guidance, and immunosuppression should be tailored to patient's immunologic risk and tolerance of medications*</b></p> <p><u>Laboratory Monitoring:</u></p> <ul style="list-style-type: none"> <li>• Recommended monitoring trough level once weekly upon initiation and with any dose changes</li> <li>• When target trough level has been attained, recommend monitoring levels once monthly</li> <li>• Monitor fasting lipids profile annually, proteinuria at 6 months and then annually post-transplant, and LFTs and CBC while on therapy.</li> </ul> |  |  |  |

|                 |                  |  |
|-----------------|------------------|--|
| Adverse Effects | Proteinuria      | <ul style="list-style-type: none"> <li>Consider administration of angiotensin-converting enzyme (ACE)-inhibitors and angiotensin II receptor antagonists and reducing mTOR levels</li> </ul>   |
|                 | Mouth ulcers     | <ul style="list-style-type: none"> <li>Development of mouth ulcers seems to be dose-related because they usually appear after the loading dose and often improve after a dose reduction</li> <li>Addition of a high-potency topical steroid may be considered</li> </ul> |
|                 | Hyperlipidemia   | <ul style="list-style-type: none"> <li>Follow current guidelines for management (diet, exercise, lipid lowering agents)</li> <li>Immunosuppressive strategies minimizing doses of mTORs, CNIs, or corticosteroids may help in controlling hyperlipidemia</li> </ul>      |
|                 | Leukopenia       | <ul style="list-style-type: none"> <li>Consider dose reduction or temporary drug suspension if appropriate</li> </ul>  |
|                 | Thrombocytopenia | <ul style="list-style-type: none"> <li>Consider dose reduction or temporary drug suspension if appropriate</li> </ul>  |
|                 | Anemia           | <ul style="list-style-type: none"> <li>Consider dose reduction or temporary drug suspension if appropriate</li> </ul>  |

UWHealth

## Prednisone – liver transplant

|                                | Recommendations  |  |   | Notes/Evidence  |  |
|--------------------------------|--|--|---|---|--|
| Initiation                     | Post-operative day 5 following dexamethasone taper   |  |   | <ul style="list-style-type: none"> <li>Prednisone 10 mg twice daily will be started on POD 5 following dexamethasone taper and may be continued on discharge</li> </ul> |  |
| Dosing (initial)               | Standard steroid taper <ul style="list-style-type: none"> <li>Prednisone taper should occur following POD5</li> <li>Assessment for prednisone taper should occur at 3-4 weeks post-operatively for patients without autoimmune disease</li> <li>Factors that may influence the duration of prednisone taper:               <ul style="list-style-type: none"> <li>Current and historical CNI levels</li> <li>Current and historical MPA dosing</li> <li>Current liver function</li> <li>Episodes of rejection</li> <li>Perceived rejection and infection risk</li> </ul> </li> </ul> | Dexamethasone  | 100 mg                                    | POD0  | <ul style="list-style-type: none"> <li>Prednisone doses should be split to twice daily dosing for patients requiring insulin for glucose control (UW Health, Very Low, Conditional)</li> <li>Patient should be off prednisone by 2 months post-transplant and maintained on tacrolimus and mycophenolate but is based on provider discretion</li> <li>For patients on doses higher than 20 mg daily for anticipated duration of greater than 2 weeks, PJP prophylaxis should be initiated</li> </ul> |
|                                |  |  | 50 mg                                     | POD1  |  |
|                                |  |  | 25 mg                                     | POD2  |  |
|                                |  |  | 12 mg                                     | POD3  |  |
|                                |  |  | 6 mg                                      | POD4  |  |
|                                |  | Prednisone   | 10 mg BID                                 | POD5  |  |
|                                |  | <i>Without autoimmune disease</i>  | Decrease by 5 mg every 2 weeks until gone |   |  |
| <i>With autoimmune disease</i> | Decrease by 5 mg every 2 weeks to a dose of 5 mg daily   |  |   |   |  |
| Labs                           | <u>Laboratory Monitoring:</u><br>Glucose, bone mineral density   |  |   |   |  |
| Adverse effects                | Hyperglycemia  | <ul style="list-style-type: none"> <li>Prednisone doses should be split to twice daily dosing for patients requiring insulin for glucose control</li> </ul>  |   |   |  |
|                                | Heartburn/reflux   | <ul style="list-style-type: none"> <li>Start a proton pump inhibitor (PPI) at time of transplant</li> <li>If a patient complains of heartburn on daily dosing of the PPI, frequency may be increased to twice daily (pending renal function)</li> <li>Discontinue PPI in patients with no history of heartburn/gastroesophageal reflux disease (GERD) prior to transplant if prednisone is discontinued</li> </ul> |   |   |  |
|                                | Osteoporosis   | <ul style="list-style-type: none"> <li>Recommend calcium 1200 mg daily (based on elemental calcium dosing)</li> <li>Recommend vitamin D 2000 units daily</li> </ul>  |   |   |  |