Our Lady of the Lake Regional Medical Center – Adult Tacrolimus Pharmacy Consult Protocol and Training Module

Introduction

Background

Tacrolimus (also known as "FK", "FK506", or by the brand name Prograf®) is a calcineurin inhibitor that is one of the agents of choice for the prevention of solid organ transplant rejection. Its properties result in potent inhibition of T-lymphocyte activity; thus, it is indicated following kidney, liver, heart, and other solid organ transplants. Tacrolimus is generally prescribed in combination with mycophenolate and/or prednisone as a potent immunosuppressing "cocktail" after undergoing transplant.

Pharmacogenomics

As a narrow therapeutic index agent that is susceptible to metabolic variation secondary to genotypic variation, tacrolimus requires therapeutic drug monitoring. Genetic polymorphisms of CYP3A5 result in significant variability in tacrolimus dosing from patient to patient.

Adverse Effects

Common adverse effects include renal toxicity, neurotoxicity, metabolic abnormalities (e.g. new-onset diabetes mellitus), and electrolyte abnormalities. Notably, renal toxicity and neurotoxicity are thought to be associated with Cmax concentrations, while metabolic abnormalities are concentration independent.

Pharmacokinetics

Absorption

Oral absorption of tacrolimus is variable and incomplete, with bioavailability ranging from 9%-43%. Metabolism via CYP3A4 and gastric motility among other factors will affect the absorption of tacrolimus. The manufacturer makes no recommendation for taking tacrolimus with regard to food, however concomitant administration of meals results in a reduced rate and extent of absorption.

Distribution

Partitioning of tacrolimus between plasma and blood depends on hematocrit, current tacrolimus concentration, plasma protein concentration, and sample temperature. Tacrolimus is highly protein bound (99%) in the plasma. Whole blood volume of distribution is approximately 0.85-1.94 L/kg.

Metabolism and Excretion

Tacrolimus undergoes extensive CYP3A metabolism with primary elimination in the feces. Less than 1% of an IV dose is excreted unchanged in the urine.

The elimination half-life is variable (4-41 hours) for both oral and intravenous dosage forms, though the mean is approximately 12 hours. Due to this large variability, dose changes may take several days to reach steady state.

Drug Formulations

It is important to note that several of the commonly-prescribed transplant medications have multiple dose formulations, many of which are **NOT** interchangeable. The table below outlines available tacrolimus dosing formulations:

Tacrolimus			
Formulation	**Brand name**	**Formulary Status**	**Notes**
Capsule – immediate release	Prograf®	Formulary	0.5 mg, 1 mg, 5 mg capsules
Oral suspension	-	Formulary	0.5 mg/mL compounded
IV solution	-	Formulary	5 mg/mL vials
Capsule – extended release	Astagraf XL®	Non-formulary	0.5 mg, 1 mg, 5 mg capsules
Tablet – extended release	Envarsus XR®	Non-formulary	0.75 mg, 1 mg, 4 mg tablets
Granules	Prograf®	Non-formulary	1 mg unit dose granules

Note: IV tacrolimus is RARELY indicated. Patients who are NPO (feeding tube, intubated, etc.) can receive tacrolimus sublingually at **half the PO dose** as discussed on page 4

Goal Levels

Patient-specific goal tacrolimus troughs are to be determined by patient's primary, outside transplant, or specialist team

The table below is a general guide to recognizing goal tacrolimus levels in post-transplant patients. A final determination will come from discussions with the patient's specialist (outside facility transplant team, nephrology, gastroenterology, etc.).

Typical Goal Tacrolimus Troughs									
	Kidney & Pancreas			*Liver*			*Heart & Lung*		
# Months Post Transplant	*0-3*	*3-12*	*>12*	*0-3*	*3-6*	*>6*	*0-3*	*3-6*	*>6*
Goal Trough (ng/mL)	7-10	6-8	3-5	10-12	8-10	6-8	8-15	8-12	5-10

Note: Goal level may change during admission. The specialist team may determine a lower goal to be more appropriate for a patient with a severe infection, while a higher goal may be appropriate if there is suspicion of acute rejection. Daily communication with the care team is required.

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Pharmacy Consults

Pharmacy will follow all tacrolimus orders while admitted. Levels can be ordered as needed by a pharmacist at any time.

Automatic Consults

Pharmacy will be automatically consulted on tacrolimus orders while a patient is admitted, with special consideration taken for renal transplant patients.

All tacrolimus adjustments for renal transplant patients will be made in consultation with a nephrologist. For all renal transplant recipients on tacrolimus, the pharmacist will contact the nephrology team (including if nephrology has yet to be consulted) to discuss the patient and accompanying recommendations. At this time the pharmacist will request a consult from the nephrologist to assist with adjustment of tacrolimus regimens.

Once a tacrolimus order and accompanying pharmacy consult is entered, a pharmacist may adjust a tacrolimus regimen in addition to ordering tacrolimus and serum creatinine levels as needed. Once an order is entered, gather the following information to appropriately assess a patient:

1. Type of transplant
2. Approximate year of transplant
3. Concomitant transplant medications (mycophenolate, steroids, etc.)
4. Current home dose
    a. AM dose
    b. PM dose
    c. Dosage form
    d. Route
5. Patient's outpatient follow up provider (transplant team, nephrology, endocrinology, etc.)
6. Patient's outpatient goal level

Ordering Levels

Tacrolimus dose adjustments should be based on an 11-hour trough level. A non-trough level may be drawn upon admission (to ensure home adherence, evaluate for toxicities, etc.) if deemed necessary.

Tacrolimus levels should be ordered at the following intervals:

- **Once** upon admission
- **Daily** troughs when making dose adjustments
- **Once weekly** troughs when two therapeutic levels have been achieved

Note: tacrolimus levels may take up to **3-7 days** to reflect dose changes.

Dose Adjustments

If trough level is BELOW goal:

- If ≥50% below target goal, increase daily dose by about 25-50%

- If <50% below target goal, increase daily dose by about 25%

If trough level is ABOVE goal:

- If ≥50% above target goal, decrease daily dose by about 25-50%
- If <50% above target goal, decrease daily dose by about 25%
- If ≥50% above target goal AND SCr has increased by ≥ 0.3 mg/dL over baseline, consider holding a dose or ordering a trough level prior to the next dose

Note: dialysis or new initiation of dialysis generally does not affect tacrolimus levels

Administration

Dosing Schedule

Doses must be administered separate from meals to facilitate proper absorption. All doses must be adjusted to the following schedule:

	Tacrolimus Dosage and Administration Form	
	Oral capsules/tablets	**Sublingual**
AM Dose	0500	0500
PM Dose	1700	1700

Oral Solution Administration

Oral solution should not be administered via enteral feeding tube. Tacrolimus is known to have high absorption into PVC and non-PVC-based tubing. Once multiple doses are administered via enteral tube, the tubing becomes saturated and will then deliver a supratherapeutic dose of medication to the patient.

Sublingual Administration

- Open capsule and sprinkle contents under the tongue
- Sublingual route may be used for ANY patient regardless of intubation or diet status
- Sublingual dose is approximately one half of the oral dose (e.g. if patient is currently prescribed 1 mg PO BID, the sublingual equivalent will be 0.5 mg SL BID)
- In the administration comments section of the Epic order use the dot phrase ".SLtacro" which reads:

> "Open capsule and sprinkle contents under the tongue, regardless of intubation or diet status. Please use appropriate PPE as follows: double chemo gloves, protective gown, and respiratory protection."

Drug-Drug Interactions[+]

No adjustments are needed if patient has been stable with therapeutic levels on both medications.

Medications that DECREASE tacrolimus levels	Adverse effects	Management
Anticonvulsants		
• Phenytoin* • Carbamazepine • Phenobarbital* • Primidone*	Decreased tacrolimus effectiveness. May lead to rejection.	Increase tacrolimus dose by 30% and monitor levels following the addition of anticonvulsant
Antimicrobials		
• Rifampin* • Rifabutin	Decreased tacrolimus effectiveness. May lead to rejection.	Monitor tacrolimus levels

Medications that INCREASE tacrolimus levels	Adverse effects	Management
Antidepressants		
• Fluoxetine* • Fluvoxamine* • Paroxetine • Mirtazapine • Venlafaxine • Sertraline	Decreased tacrolimus metabolism (increased risk of toxicity)	• Consider citalopram or escitalopram • Monitor tacrolimus levels
Antimicrobials		
• Erythromycin* • Clarithromycin*	• Decreased tacrolimus metabolism • Increased rate of tacrolimus absorption	• Monitor tacrolimus levels • Monitor SCr
• Azole antifungals	Decreased tacrolimus metabolism (increased risk of toxicity	• Monitor tacrolimus levels • Monitor SCr
Cardiovascular		
• Diltiazem* • Verapamil* • Amiodarone*	Decreased tacrolimus metabolism (increased risk of toxicity)	Monitor tacrolimus levels
HIV Medications		
• Protease inhibitors	Decreased tacrolimus metabolism (increased risk of toxicity)	Monitor tacrolimus levels

Medications that increase risk of QTc prolongation with tacrolimus	Management
Antiarrhythmics	
• Amiodarone* • Procainamide*	• If possible, select alternative agent • Monitor QTc
Antimicrobials	
• Ciprofloxacin* • Amphotericin B • Azithromycin • Levofloxacin	• Select alternative agent if major interaction • Monitor QTc
Antipsychotics	
• Chlorpromazine* • Ziprasidone* • Haloperidol • Quetiapine	• Select alternative agent if major interaction • Monitor QTc

+ This table lists the most common agents that may be encountered and is not a comprehensive list
* Indicates a major interaction

Toxicity

Symptoms of tacrolimus toxicity vary widely from no symptoms to renal failure and neurotoxicity. The most common symptoms are listed in the table below.

Symptoms of Tacrolimus Toxicity	
Nausea	SCr increase
Headache	Renal failure
LFT increase	Neurotoxicity (seizure, AMS)
Electrolyte disturbances	Tremor

References

1. Murphy JE. *Antirejection agents*. Clinical Pharmacokinetics. 5th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2012. 159-167.
2. Connor TH, MacKenzie BA, DeBord DG, et al. *NIOSH list of antineoplastic and other hazardous drugs in healthcare settings.* U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2016. 25. Accessed July 31, 2020. https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf
3. Prograf. Package insert. 2019.
4. Jantz AS, Patel SJ, Suki WN, et al. Treatment of acute tacrolimus toxicity with phenytoin in solid organ transplant recipients. Case Reports in Transplantation; 2013.
5. Jin SE, You S, Jeon S, Byon HJ, Hwang SJ. Evaluation of Drug Sorption to PVC- and Non-PVC-based Tubes in Administration Sets Using a Pump. *J Vis Exp*. 2017;(121):55086. Published 2017 Mar 11. doi:10.3791/55086
6. Costanzo MR, Dipchand A, Starling R, et al. The international society of heart and lung transplantation guidelines for the care of heart transplant recipients. J Heart Lung Transplant; 2010.
7. Domenech L, Guiu Segura JM, Montoro Ronsano JB, et al. Sublingual and enteric tacrolimus whole blood levels in an intensive care unit. Eur J Hosp Pharm

ADULT TACROLIMUS PHARMACY CONSULT QUICK REFERENCE

Consults

- All patients on tacrolimus will be monitored by pharmacy
- All renal transplant patients on tacrolimus will have tacrolimus monitored and adjusted by pharmacy in consultation with a nephrologist
    - Pharmacists will contact nephrology to discuss the patient, clarify goal trough, and request a consult to adjust tacrolimus regimens
    - Any tacrolimus order with a non-renal transplant indication will have an automatic consult for pharmacy to dose tacrolimus
- A consult from a physician must include goal trough (which may change during the patient's stay) and who the preferred contact/team is for follow up. Physicians may require assistance from the pharmacist in contacting outside providers to determine the goal trough.
- Daily communication with a physician is required to determine if goal levels require updating
- When home tacrolimus is reordered, a line will populate in the "Best Practices" folder. **The pharmacist must then enter a formal consult with that will transfer into the "Consult Basket".**

Medication History

Gather the following information to properly assess a patient:

1. Type of transplant
2. Approximate year of transplant
3. Concomitant home transplant medications (mycophenolate, steroids, etc.)
4. Current home dose
    a. AM dose
    b. PM dose
    c. Dosage form
5. Patient's follow up provider (transplant team, nephrology, endocrinology, etc.)
6. Patient's outpatient goal level

Daily Monitoring

- A note addressing the initial consult must be written within 24 hours
- A progress note addressing any change in the tacrolimus regimen must be written within 24 hours of the change
- Templates for tacrolimus consult documentation can be found using the following dot phrases:
    - .tacroinitial
    - .tacroprogress
    - .tacrodaily

Formulation Considerations

- SL tacrolimus dose = ½ PO dose
- If NPO, convert oral to sublingual
- Oral solution should **NOT** be administered via enteral feeding tube (tubing absorbs solution then delivers high dose once saturated)
- Envarsus XR may be switched to formulary tacrolimus immediate release product (see Envarsus XR website for calculator or adjust based on estimation that Envarsus XR dose is 80% of tacrolimus IR dose)

Standard Times

	Lab Draw	Dose Administration
AM	0400	0500
PM	1600	1700

*Tacrolimus levels are batched by lab once daily at 1100

Levels and Adjustments

- Levels will be ordered on the following basis:
  - **Once** upon admission
  - **Daily** trough when making dose adjustments or after the initiation or discontinuation of CYP3A inducers/inhibitors
  - **Weekly** trough when two therapeutic levels have been achieved
- Adjust dose one daily administration at a time (e.g. adjust AM dose only, then consider adjusting PM dose if additional adjustment needed at next level check)
- Consider capsules patient already has at home

If level is BELOW goal:

- If ≥50% below target goal, increase daily dose by about 25-50%
- If <50% below target goal, increase daily dose by about 25%

If level is ABOVE goal:

- If ≥50% above target goal, decrease daily dose by about 25-50%
- If <50% above target goal, decrease daily dose by about 25%

If ≥50% above target goal AND SCr has increased by ≥ 0.3 mg/dL over baseline, consider holding a dose or ordering a trough level prior to the next dose

Contact Information

Transplant Institution/Clinic	Phone Number	Location
Renal Associates of Baton Rouge	225-767-4893	5131 O'Donovan Dr Suite 100, Baton Rouge, LA 70808
Ochsner New Orleans	504-842-3925	1514 Jefferson Highway, New Orleans, LA 70121
Tulane New Orleans	504-988-5344	1415 Tulane Ave, New Orleans, LA 70112
Tulane Northshore at Lakeview Regional Medical Center	985-867-4223	101 Judge Tanner Blvd Suite 404, Covington, LA 70433

Appendix I: Pharmacy tacrolimus consult service

Certification

OLOL pharmacists must be certified as per current department and hospital policy prior to independent utilization of this protocol. Pharmacists not yet certified must gain approval from a certified pharmacist prior to making any adjustments or recommendations.

Consultation Process

1. All patients on tacrolimus will be monitored by pharmacy
2. All renal transplant patients on tacrolimus will have tacrolimus monitored and adjusted by pharmacy in consultation with a nephrologist
   - Pharmacists will contact nephrology to discuss the patient, clarify goal trough, and request a consult to adjust tacrolimus regimens
   - Any tacrolimus order with a non-renal transplant indication will have an automatic consult for pharmacy to dose tacrolimus
3. Once consulted, pharmacists will evaluate, adjust, and monitor tacrolimus daily for the patient on which the consult was placed until the tacrolimus is discontinued.
4. The pharmacist will assess the patient and evaluate the appropriateness of the current drug regimen, potential for toxicity, current dose, lab sampling times, previous levels, or the need for future levels.
5. The pharmacist is responsible for ordering tacrolimus levels and other monitoring parameters, such as serum creatinine, as indicated.
6. The pharmacist will adjust initial and subsequent dosing regimens based on a patient's dosing history, discussion with treating physicians/specialists, dosing guidelines for tacrolimus, and/or interpretation of blood levels including analyzing the validity of blood concentrations and collection times.

Documentation

1. The certified pharmacist receiving the consult will enter an initial consult note in the patient's EMR within 24 hours using the "Tacrolimus Initial Consult Note" template to acknowledge the consult, notify providers of pharmacist monitoring, and communicate plans for dosing and monitoring.
2. Additional notes will be entered within 24 hours of a tacrolimus dosing regimen change using the "Tacrolimus Progress Note" template
3. Notes should contain all relevant patient information and pharmacokinetic parameters necessary to justify and communicate dosing and monitoring recommendations.
4. The pharmacist will initiate a daily monitoring form to communicate with other pharmacists using "Tacrolimus Daily Monitoring Form" template. Relevant information and a daily update should be maintained here in an organized fashion to facilitate continuity of care in the event that a patient is transferred to another area of the hospital or another pharmacist will manage the patient's medication therapy.

Monitoring Parameters

1. A pharmacist will assess the following parameters daily to assess appropriateness of current therapy:
    a. Indication and goals of therapy (target trough levels)
    b. Patient's clinical status
        i. Changes in renal function
        ii. Changes in administration routes
    c. Pertinent past medical history
        i. Transplanted organ
        ii. Transplant year
        iii. Reason for transplant
        iv. Transplant and follow up institutions
        v. Current home provider managing transplant
    d. Potential drug interactions with tacrolimus and newly-initiated medications
    e. Concomitant immunosuppressants
        i. Mycophenolate
        ii. Steroids
    f. Dose and administration times
    g. Tacrolimus levels and times they were obtained