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**Policy: Kidney/Pancreas Post Transplant: AUC Monitoring of Tacrolimus Levels in Post Renal Transplant Patients (Area Under the Curve)**

**Statement: Vision Strategy:** Patient Care

**Policy Statement:** The Emory Transplant Center and all the solid organ transplant programs will comply with all applicable federal, state, and local laws, regulations, policies and protocols regarding the management of transplant patients.

**Basis:** Tacrolimus is a potent immunosuppressive agent used in immunosuppressive therapy in transplant patients. High blood levels of tacrolimus appear to be associated with serious adverse events such as nephrotoxicity, neurotoxicity, and hyperglycemia. Subtherapeutic levels of tacrolimus are associated with an increased risk of acute rejection. More intense therapeutic drug monitoring may be useful in selected patients to optimize immunosuppression therapy.

**Admin Responsibility:** All transplant program physicians, practitioners and clinical staff members are responsible for compliance with this clinical protocol.

**Activation Date: 05.24.2017**

**Scope/Procedure:**

1. Background

Tacrolimus has a narrow therapeutic index and wide variability in absorption and metabolism. Consequently, therapeutic drug monitoring is recommended. Typically, trough levels of tacrolimus are used to assess efficacy and toxicity. However, some patients have difficulty achieving therapeutic levels of tacrolimus and/or experience tacrolimus toxicity. These patients may benefit from more intense therapeutic drug monitoring by collecting and calculating and abbreviated area under the curve (AUC), which may be more representative of total drug exposure than trough levels.

1. Criteria for Monitoring Area Under the Curve
Any recipient receiving tacrolimus with the following clinical findings may have AUC levels:

a. Suspicion of or biopsy proven calcineurin inhibitor toxicity
b. Inability to achieve targeted 12 hour trough tacrolimus level despite apparent adequate/high dosing and appropriate adherence
2. Assistance with Calculating Area Under the Curve and Adjusting Doses
	1. For patients requiring an AUC to be measured, a pharmacotherapy consult should be initiated by contacting a kidney transplant pharmacist to assist with calculations and dosing.
3. Monitoring and Calculating AUC requires 4 (four) blood samples drawn at the following times:
1- Trough Level: Before AM dose (T0)
2- 1 hr. post dose (T1)
3- 2 hr. post dose (T2)
4- 4 hr. post dose (T4)
AUC is calculated as: 10 + 1.4 (T0) + 0.8 (T1) + 1.6 (T2) + 5.5 (T4)
4. Correlating Tacrolimus AUC and Trough Levels

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| Goal Tacrolimus Trough | Correlating Tacrolimus AUC |
| 8 – 12 | 150 – 225 |
| 5 – 8 | 100 – 150 |
| 3 – 5 | 50 – 100 |

After calculating AUC based on the patient’s level, compare the AUC to the correlating tacrolimus trough and trough that was drawn prior to dose. Tacrolimus troughs are sometimes not representative of overall drug exposure and do not necessarily correlate with the expected AUC. Therefore, dose adjustments may need to be made or additional medications may need to be added to increase levels of tacrolimus.

1. Guidance on Strategies for Achieving Target Tacrolimus Levels
	1. AUC that correlates with higher trough level than the measured trough level
		1. If the peak (T1-T2) and AUC are high, but the measured trough is lower than goal, this may indicate a “rapid metabolizer” of tacrolimus. These patients may benefit from inhibition of tacrolimus metabolism via a CYP inhibitor (such as ketoconazole). Please see section VII for assistance initiating an inhibitor.
	2. AUC that correlates with a trough that is lower than goal
		1. Low drug exposure may indicate poor absorption. In some cases, taking tacrolimus on an empty stomach may help patients achieve goal troughs.
		2. Increasing the tacrolimus dose may be warranted to achieve goal troughs depending on the how close the measured trough level and AUC are to goal

The following equation may be utilized to aid in tacrolimus dose adjustments:

New Dose = Current Dose x (AUCtarget/AUCcurrent)

* + 1. Patients with very low AUCs or patients who are having side effects (such as tremors, headaches, and nausea) may benefit from the addition of an inhibitor if therapeutic levels cannot be achieved with dose adjustments. Please see section VII for assistance initiating an inhibitor.
1. Inhibitor Initiation

If target tacrolimus trough levels are not achieved with dose adjustments after obtaining an AUC, an inhibitor such as ketoconazole may be considered to boost tacrolimus levels. Ketoconazole prevents the metabolism of tacrolimus by inhibiting the enzyme cytochrome P 450 3A4 which plays a major role in metabolism.

1. Initiate ketoconazole 100 mg PO daily
2. Consider reducing tacrolimus dose based on current trough level and goal trough level
	1. Typically, the use of ketoconazole results in a decrease of tacrolimus dose of about 50% to achieve the same level, however, this does not hold true in all patients. Because patients contain different levels of CYP 3A4 the effect of adding an inhibitor can be variable.
3. Monitor troughs closely. Check a tacrolimus trough within one week.

**References:** 

Approved by: Renal (Pancreas) Transplant Leadership Group

\_\_\_Signature on File\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
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Chair, Renal Transplant Leadership Group
Director, Renal and Pancreas Transplant Programs

Approval: 12/02/2009

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| **Regulatory References:**1. Scholten E et al. AUC-guided dosing of tacrolimus prevents progressive systemic overexposure in renal transplant recipient. Kidney International 2005;67:2440-2447.
2. Gais E et al. Tacrolimus population pharmacokinetics and Bayesian estimation in Tunisian renal transplant recipients. International Journal of Pharmacy and Pharmaceutical Sciences 2013;5:108-115.
3. Wong K et al. Abbreviated tacrolimus area-under-the-curve monitoring for renal transplant recipients. American Journal of Kidney Disease 1999;35:660-666.
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**Related Policies/Procedures:**

**Policy: Kidney/Pancreas Post Transplant Management Protocol of the Renal Transplant Recipient (Outpatient)**

**Policy: Kidney/Pancreas Post Transplant Medication Management Protocol**

**Policy: Kidney/Pancreas Post Transplant Recipient Medication Minimization Clinic Protocol**

**Approved By**
**Transplant Leadership Group**

**Key Words For Search: therapeutic drug monitoring, AUC, area under the curve, inhibitor**

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