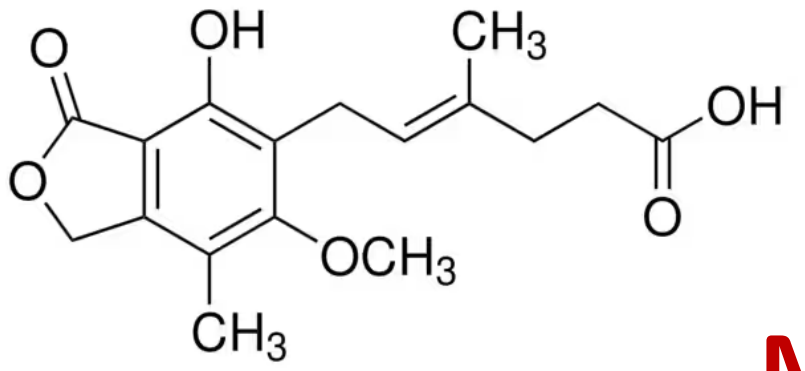
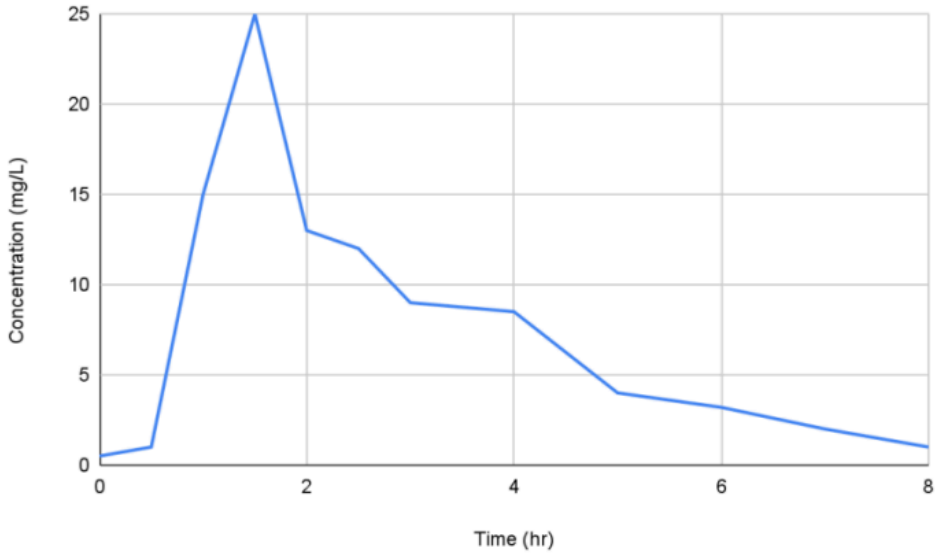


Evidence Scan

Extra Corporeal Nephrology Group

Mycophenolic Acid AUC Monitoring

Does AUC Monitoring Improve Outcomes?



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Background

- Mycophenolic Acid (MPA) is vital for preventing rejection in kidney transplantation but has highly variable absorption and metabolism
- Currently, two mycophenolate compounds are available, mycophenolate mofetil and enteric-coated (EC) mycophenolate sodium. Mycophenolate mofetil and EC-mycophenolate sodium are essentially completely hydrolysed to MPA by esterases in the gut wall, blood, liver and tissue.
- Area Under the Curve ($AUC_{0-12}h$) represents total drug exposure, hypothesized to correlate better with outcomes than trough levels (C0).
- Commonly Cited Therapeutic Target: While debated and context-dependent, many studies investigate or reference a target MPA $AUC_{0-12}h$ range of 30-60 mg·h/L.
- Aim of this mini review: Review key study findings linking MPA AUC to efficacy and toxicity in kidney transplantation

MPA AUC & Preventing Rejection

Multiple studies suggest MPA exposure below a certain threshold increases the risk of acute rejection (AR).

- Van Gelder et al. (2001): Found patients with AR often had AUCs < 30 mg·h/L.
- Staatz & Tett (2007): Supported the 30-60 mg·h/L target range, noting inconsistencies and confounders.
- Kuypers et al. (2007): AR patients had significantly lower mean AUC, especially early post-transplant.

Summary: AUC < 30 mg·h/L frequently linked with increased risk of AR

MPA AUC & Safety: Minimizing Adverse Events

Excessive MPA exposure is linked to dose-limiting toxicities.

- Shaw et al. (2003): Higher AUC associated with leukopenia and GI side effects (toxicity thresholds ~>50-60 mg·h/L).
- Filler et al. (2004): High AUC correlated with hematological toxicity in pediatric recipients.
- Observational Studies: Higher infection, diarrhea, and leukopenia at AUC > 60 mg·h/L.

Summary: AUC > 60 mg·h/L often linked to increased adverse events.

Does AUC Monitoring Improve Outcomes? Comparative Evidence

- Le Meur et al. (2007, APOMYGRE Trial): AUC-targeting reduced out-of-range patients, fewer rejections/toxicity (not always statistically significant).

- Thomson et al. (2011, FDCC Study): Better target attainment with AUC monitoring, but outcome differences limited.

Summary: AUC monitoring enhances exposure accuracy; clinical benefits are suggestive, not definitive.

Summary of Evidence and Implications

Consistent Findings:

- AUC < 30 mg·h/L linked with higher rejection risk.
- AUC > 60 mg·h/L associated with increased toxicity.
- 30-60 mg·h/L emerges as a common therapeutic target.

Challenges:

- Study heterogeneity and AUC measurement variability.
- Practical barriers to full AUC monitoring
- Lack of large RCTs proving long-term survival benefit.

Clinical Bottom Line: AUC is the most informative PK parameter for MPA. Use selectively in high-risk or problematic cases.

Sampling Protocol for Mycophenolic Acid AUC_{0-8} Monitoring

Therapeutic drug monitoring (TDM) of MPA is typically guided by AUC_{0-12}, but AUC_{0-8} is easier for outpatient/clinical workflow, but may miss enterohepatic recirculation peak

- Mycophenolate mofetil and EC-mycophenolate sodium to be taken at leat 1 hour before breakfast
- Blood samples are collected at the following time points after the morning dose:
- Trough (0 h), 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 7h, and 8h
- To facilitate this, the patient can be in a day care unit with a peripheral IV cannula with heparin lock to avoid multiple venipunctures. Based on the 12 concentration values, the AUC_{0-8} is calculated to guide individualized dosing.

Sample Mycophenolic Acid AUC_{0-8} Report

Therapeutic Drug Monitoring: Mycophenolic Acid **Date of Procedure: 15/04/2025**

Concentrations estimated at: Analytical Chemistry Laboratory

Name: [redacted] UHID: [redacted] Phone: [redacted]

Age (yrs): 21 Sex: M Weight (kg): 61 Height (cm): 168

Dose (mg): 1000 mg – 1000 mg Brand: Cellcept Date of Transplant: 21/01/2025

Diagnosis: Post Renal Transplant Department: Nephrology

Co-medications: Tacrolimus, Prednisolone, Carvedilol, Clonidine, Cilnidipine, Metformin, Pantoprazole, Calcium, Magnesium oxide, Lactulose, Sulfamethoxazole, Trimethoprim, Valgancyclovir, Insulin

MPA trough = 7.17 mg/L **Extrapolated MPA $AUC_{12\ hr}$** = 120.4 mg.h/L

Comments: Patient had one episode of vomiting on the day of the test following lunch. But he did not vomit the medicine. This is unlikely to influence the test report. No previous history of vomiting or diarrhea. Please consider reducing the dose to keep AUC less than 60 mg.h/L. Suggest to reduce the dose to 500 mg – 750 mg.

Therapeutic range for $AUC_{12\ hr}$| Lupus Nephritis: 45 - 90 mg.h/L, Solid Organ transplant: 30 - 60 mg.h/L

Reference: https://doi.org/10.1136/lupus-2023-001093