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Utility of Monitoring Mycophenolic Acid in Solid Organ Transplant Patients

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov**.

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Our editorial staff, Cecile Royer, Roxanne Cheeseman, and Sarah Smith, have provided invaluable input into this document.

Structured Abstract

Objectives: To investigate whether monitoring concentrations of mycophenolic acid (MPA) in the serum or plasma of persons who receive a solid organ transplant will result in a lower incidence of transplant rejections and adverse events versus no monitoring of MPA. To investigate whether the incidence of rejection or adverse events differs according to MPA dose or frequency, type of MPA, the form of MPA monitored, the method of MPA monitoring, or sample characteristics. To assess whether monitoring is cost-effective versus no monitoring.

Data Sources: The following databases were searched from their dates of inception (in brackets) until October 2007: MEDLINE® (1966); BIOSIS® Previews (1976); EMBASE® (1980); Cochrane Database of Systematic Reviews® (1995); and Cochrane Central Register of Controlled Trials® (1995).

Review Methods: Studies identified from the data sources went through two levels of screening (i.e., title and abstract, full text) and the ones that passed were abstracted. Criteria for abstraction included publication in the English language, study design (i.e., randomized controlled trial [RCT], observational study with comparison group, case series), and patient receipt of allograft solid organ transplant. Additionally, any form of MPA had to be measured at least once in the plasma or serum using any method of measurement (e.g., $AUC_{0\text{-}12}$, C_0). Furthermore, these measures had to be linked to a health outcome (e.g., transplant rejection). Certain biomarkers (e.g., serum creatinine, glomular filtration rate) and all adverse events were also considered health outcomes.

Results: The published evidence on MPA monitoring is inconclusive. Direct, head-to-head comparison of monitoring versus no monitoring is limited to one RCT in adult, kidney transplant patients. Inferences about monitoring can be made from some observational studies, although the evidence is equivocal for MPA dose and dose frequency, nonexistent for type of MPA, inconclusive for form of MPA monitored or method of monitoring, and nonexistent for cost-effectiveness. Some studies suggest gender and concomitant use of calcineurin inhibitors will affect pharmacokinetic parameters, but the impact of these findings has not been assessed in relation to monitoring versus no monitoring.

Conclusion: The state of knowledge about therapeutic drug monitoring of MPA in solid organ transplants is still in its infancy. Until there is more evidence on the utility of routine MPA monitoring in solid organ transplant recipients, patients, clinicians, and other stakeholders (e.g., public and private insurers) will have to decide on a case by case basis whether the possible but uncertain benefits are worth the extra time and expense of monitoring.

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Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm.

Executive Summary

Introduction

Mycophenolic acid (MPA) is an immunosuppressant drug used to prevent rejection of solid organ transplants. The drug is marketed as the ester prodrug mycophenolate mofetil (MMF)(CellCept®) for kidney, liver, and heart transplants or enteric-coated mycophenolate sodium (Myfortic®) (ECMPS) for kidney transplants.[1]

Therapeutic drug monitoring of MPA has the objective of improving control over acute rejection. It is based on observed associations between pharmacokinetic (PK) parameters such as total MPA area under the concentration-time curve (AUC_{0-12}) and acute rejection in adult and pediatric patients.[2,3]

This evidence report was commissioned to address the following key questions:

1. What is the evidence that monitoring mycophenolic acid in patients who receive a solid organ transplant results in a lower incidence of transplant rejections and adverse events compared to patients who are not monitored?

2. Does the incidence differ by any of the following?
   a) MPA dose and dose frequency;
   b) Type of MPA (mycophenolate mofetil [CellCept®], enteric-coated mycophenolate sodium [Myfortic®]).

3. a) Does the incidence differ by any of the following?
      ia) Total versus free MPA
      ib) Albumin versus MPA

      iia) MPAG, AcMPAG versus MPA
      iib) Genetic basis of differences in MPA pharmacokinetic parameters

      iii) Assay method (HPLC, EMIT, HPLC-MS, other)

   b) Does the incidence differ by analytical method of MPA monitoring?
      i. Full AUC
      ii. Limited sampling strategies
         a. Predose concentrations
         b. 2h post dose concentrations
         c. Other

4. Does the evidence for monitoring MPA differ by any of the following?
   a) Age
   b) Gender
   c) Ethnicity
   d) Concomitant use of calcineurin inhibitors (e.g., tacrolimus, cyclosporine)
   e) Concomitant use of other medications
   f) Comorbidity

5. What is the short- and long-term cost-effectiveness of avoiding acute rejection due to MPA monitoring?

Methods

The following electronic databases were searched up until October 22, 2007:

1. MEDLINE® (1966-);
2. BIOSIS® Previews (1976-);
3. EMBASE® (1980-);
4. Cochrane Database of Systematic Reviews® (1995-);
5. Cochrane Central Register of Controlled Trials® (1995-).

We examined the reference lists of several recently published review articles[3-6] and consulted with the technical expert panel to identify additional published studies.

Inclusion/exclusion criteria. We included randomized controlled trials, observational studies with comparison groups, or case series, published in the English language. We included studies of pediatric and adult patients who received allograft solid organ transplants, provided that any form of MPA was measured in serum or plasma, using any method of measurement (e.g., AUC).

Data Collection and Reliability of Study Selection. A team of trained raters applied the inclusion and exclusion criteria to the citations identified in the literature search. Each citation was screened by two independent raters and had to pass two levels of screening (title and abstract, full text) prior to data abstraction.

Quality Assessment of Included Studies. The methodological quality of included studies was assessed independently by two raters using 'core' criteria enumerated in the draft Evidence-based Practice Centre Methods Manual (under preparation by the AHRQ).

Results

The literature search yielded 11,642 citations, from which 495 (4 percent) proceeded to full text screening. Of these 495 citations, 89 (18 percent) were included in the report and abstracted.

What is the Evidence That Monitoring Mycophenolic Acid in Patients who Receive a Solid Organ Transplant Results in a Lower Incidence of Transplant Rejections and Adverse Events Compared to Patients who are not Monitored?

Only three studies addressed this question (four reports).[7-10] Patients in the concentration-controlled group had fewer rejections than patients in the fixed-dose group in two studies (no p-value reported in one study; p=0.01 in the other study). In the third study, there were more rejections in the concentration-controlled group (p>0.05).

Does the Incidence Differ by MPA Dose and Dose Frequency?

Only one study compared rejection outcomes for subjects with planned dose adjustments based on different target MPA plasma concentrations.[11,12] In this RCT of kidney transplant recipients, the incidence of biopsy-proven acute rejection was inversely associated with increasing pre-defined MPA AUC concentration-control levels (p=0.043).

Does the Incidence Differ by Type of MPA (Mycophenolate Mofetil, Enteric-coated Mycophenolate Sodium)?

There was no evidence in the included studies to answer this question.

Does the Incidence Differ by Total versus free MPA, Albumin, Genetic Differences, Metabolites?

Free versus total MPA. The incidence of rejection or adverse events was found to differ significantly between free and total MPA in only one[13] of nine studies[13-21] that examined both forms of MPA.

Albumin. Studies generally found that impaired kidney function and hypoalbuminemia were associated with increased concentrations or AUCs of free MPA, but not total MPA.

Pharmacogenetic. Seven days after transplantation, renal allograft recipients (n=9) without the C-24T Single Nucleotide Polymorphisms (SNP) of the multidrug resistance-associated protein 2 (MRP2), but with mild liver dysfunction, had lower MPA exposure compared to MRP2 C-24T non-carriers (n=45) without liver dysfunction. MPA pharmacokinetic (PK) parameters were found to vary with the time of the day (daytime AUC > nighttime AUC). No direct associations between genotype, MPA PK parameters, and outcomes were found.

Metabolites. Two[15,16] of seven studies[15,16,20,22-25] found associations between MPA metabolite concentrations and adverse events. Higher median acyl glucuronide metabolite of mycophenolic acid (AcMPAG) (p=0.03), mycophenolic acid glucuronide (MPAG) C_0 concentrations (p=0.02), and AcMPAG/MPA ratios (p=0.004), but not higher MPA C_0 concentrations (p>0.05) were found in patients at times when they experienced anemia versus times when with no anemia.[15] The authors also found lower median MPAG C_0 concentrations at times of a leucopenia episode versus times of no episode (p=0.04). In the second study[16], a correlation was found between the amount of fecal fat loss and MPAG concentrations (r=0.9955,

p<0.001), as well as AcMPAG concentrations (r=0.90, p=0.015) in five renal allograft recipients with persistent afebrile diarrhea.

Does the Incidence Differ by Assay Method?

Only two case series[26,27] involved direct comparisons of different assay methods (enzyme-multiplied immunoassay technique (EMIT) versus high-performance liquid chromatography (HPLC)). Both reports included children with transplanted kidneys from the same research project. EMIT and HPLC were equally able to discriminate between patients with acute rejections during the first 70 days post-transplant. Decision concentrations, below which the risk of acute rejection is increased, were higher with EMIT than with HPLC. None of the PK parameters, regardless of assay method, were associated with the incidence of adverse events.

Does the Incidence Differ by Analytical Method of MPA Monitoring?

Ten studies (11 reports)[11,12,17,26-33] showed AUC_{0-12} to be related to rejection, while 4 studies [34-37] showed no relation. There were 17 positive studies (18 reports)[7,8,12,26,27,30,33,38-48] linking (predose, C_0, C_{min}, or C_{12}) concentration to rejection and 25 negative studies.[11,15,17,19,24,25,28,36,37,42,45,49-62] Only one study [57]found C_2 to be a significant predictor of rejection while one other study [54] did not. Eleven studies [10,17,19,26,43,49,54,57,59,63,64] found other limited sampling strategies (i.e., involving C_0, C_{20min}, C_{30min}, C_{40min}, C_1, C_{75min}, C_2, C_3, C_4, C_6, AUC_{0-9}) be related to rejection whereas 9 studies [11,13,17,26,36,51,52,54,65] found no relationship. Four studies[31,33,36,46] showed that AUC_{0-12} is associated with adverse effects, while 11 studies (12 reports)[11,12,17,26,29,32,35-37,52,66,67] showed no association. There were 18 studies[14,16,33,36,39-41,45,48,56,61,68-74] demonstrating associations between predose concentration (predose, C_0, C_{min}, or C_{12}) and adverse effects, and 24 studies (25 reports)[11,12,14,15,17,18,20,22,25,26,36,37,42,47,49,52,54,57,62,64,66,67,72,75,76] demonstrating no associations. No studies found C_2 to be a significant predictor of adverse effects and two[54,57] found no association. Five studies[33,59,65-67] found other limited sampling strategies (C_0, C_{30min}, C_{40min}, C_1, C_3, C_6) to be associated with adverse effects while 17 studies[10,11,13,17,20,21,26,36,49,52,54,57,64,66,75-77] showed the opposite.

Does the Evidence for Monitoring MPA Differ by Age, Gender, Ethnicity, Concomitant use of Calcineurin Inhibitors or Other Medications, or Comorbidity?

Some of the six factors of this question appear to influence MPA PK parameters. None of the included studies investigated whether PK parameter concentrations, stratified by each factor, were associated with outcomes such as rejection or adverse events. Regarding age, the evidence was equivocal. In pediatric populations, younger children were found to require a higher MMF dose to achieve a specified MPA concentration. When given the same dose of MMF, the MPA AUC has been reported to be lower in the elderly compared to younger adults. Regarding gender, the evidence appears to indicate that PK parameters are higher for females versus males. Race and ethnicity do not appear to influence MPA PK parameters. Calcineurin inhibitors and sirolimus are co-administered frequently with MMF and the bulk of the evidence found that exposure to MPA is higher in patients receiving tacrolimus or sirolimus compared to

cyclosporine, with lower doses of MMF required in combination with tacrolimus to achieve adequate MPA exposure. MPA PK parameters were generally higher in persons with renal insufficiency, although one study[20] found lowered MPA AUC in the early post-transplant period.

What is the Short and Long-Term Cost-Effectiveness of Avoiding Acute Rejection due to MPA Monitoring?

None of the abstracted studies contained any data on the cost-effectiveness of MPA monitoring.

Quality Assessment of Abstracted Studies

Twelve of the 89 abstracted studies were RCTs[10-12,25,28,29,34,50,51,65,68,78] and the remainder were observational studies (primarily case series). The quality of the RCTs was fair to good, although reporting of some essential features of trial design was lacking (e.g., method of randomization, blinding).

Compared to the RCTs, the 77 observational studies suffered from numerous reporting problems. Virtually all of the studies lacked reports of blinding among subjects (n=73), persons measuring MPA (n=74), and outcomes assessors (n=75). Differential losses to followup were not reported in 61 studies. The authors of only 29 studies made an attempt to control for confounding. Some aspects of reporting were good, though, as the authors of most of the observational studies described the methods used to measure MPA (n=68) and clearly defined their outcomes (n=69).

Discussion

What is the Evidence That Monitoring Mycophenolic Acid in Patients who Receive a Solid Organ Transplant Results in a Lower Incidence of Transplant Rejections and Adverse Events Compared to Patients who are not Monitored?

Three studies (four reports)[7-10] directly addressed this question, although the first study was not designed to compare monitoring versus no monitoring and the second study[9] found no evidence to suggest that monitored patients had a lower incidence of transplant rejections relative to non-monitored patients. The third study,[10] the first published RCT to compare monitoring versus no monitoring of MPA in any patient group, found a lower incidence of treatment failures in the monitored group. However, the RCT is limited to adult kidney transplant patients, so the efficacy of monitoring in other patient populations is still unknown. Likewise, the clinical applicability of the trial's limited AUC sampling strategy, or the applicability of the 40 mg*h/L MPA target dose, to these other populations is also unknown.

Does the Incidence Differ by MPA Dose and Dose Frequency?

The evidence to support an association between MMF dosage and rejection is inconclusive. Most studies were not designed to directly assess whether there was an association between

MMF dosage and rejection or adverse events. Solid clinical recommendations can only be made after further research is conducted, preferably using RCTs to compare different fixed doses and different targets for concentration control.

Does the Incidence Differ by Type of MPA?

None of the included studies directly compared ECMPS with MMF, so this question could not be answered.

Does the Incidence Differ by Total Versus Free MPA, Albumin, Genetic Differences, Metabolites?

None of the included studies confirmed the hypothesis that measurements of free MPA correlate better with outcomes than total MPA, although free (not total) MPA was found to be associated with infections and haematological adverse events in three studies.[13,14,17]

One pharmacogenetic study[79] showed that carriers of the two multidrug resistance protein (MRP2) single nucleotide polymorphisms (SNP) were protected from reduced MPA exposure in mild liver dysfunction. A second genetic study found associations between MPA and genes, genes and diarrhea, and MPA and rejection. The clinical relevance of both studies to MPA monitoring is unclear.

The studies regarding metabolites yielded few positive results.[15,16] Larger, randomized trials are necessary to establish the utility of monitoring MPA and its metabolites.

Does the Incidence Differ by Assay Method?

In two studies,[26,27] HPLC and EMIT performed similarly well in the assessment of acute rejection risk in pediatric kidney transplant patients. EMIT cut off values were higher than those derived from HPLC measurements. The study populations were pediatric patients, and it remains to be seen whether diagnostic sensitivities and specificities between HPLC and EMIT would differ in other populations.

Does the Incidence Differ by Analytical Method of MPA Monitoring?

There was no evidence to directly answer this key question.

Does the Evidence Differ by Age, Gender, Ethnicity, Concomitant Use of Calcineurin Inhibitors or Other Medications, or Comorbidity?

The evidence from the literature failed to directly address the key question. Of the studies that were included in the report, the focus was on adults and kidney transplant recipients. Few studies involved children or other solid organ transplants. Also, study findings were difficult to compare because measures of MPA in the serum or plasma sometimes exhibit large intra- and inter-patient variability over time post transplant.

What is the Short- and Long-Term Cost-Effectiveness of Avoiding Acute Rejection Due to MPA Monitoring?

The published literature contains no data on the cost-effectiveness of monitoring versus no monitoring in solid organ transplants. Therefore, it is not possible to answer this key question.

Limitations of this Evidence Report

Only English-language, published studies were included in this report, thereby introducing the possibility of publication bias. Virtually all of the included studies involved MMF rather than ECMPS. Therefore, the conclusions may not be applicable to the enteric-coated formulation.

Conclusions

The state of knowledge about therapeutic drug monitoring of MPA in solid organ transplants is still in its infancy. This is especially so for organs other than the kidney because the overwhelming majority of published studies involve kidney transplant patients. Overall, the published evidence on MPA monitoring is inconclusive; there is almost no direct evidence to suggest that monitoring would reduce the incidence of rejection or adverse events in any solid organ transplant. Each of the key questions in this report would be more adequately addressed using RCTs.

Clinical recommendations. There is almost no direct evidence to suggest that monitoring is more or less beneficial than not monitoring. Until there is more evidence on the utility of routine MPA monitoring in solid organ transplant recipients, patients, clinicians, and other stakeholders (e.g., public and private insurers) will have to decide on a case by case basis whether the possible but uncertain benefits are worth the extra time and expense of monitoring.

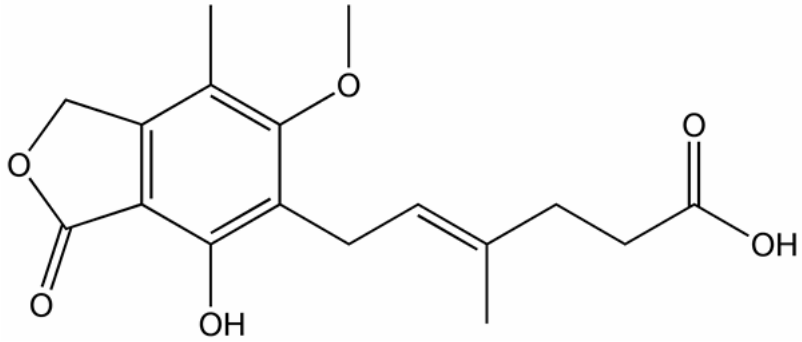
Evidence Report

Chapter 1. Introduction

Mycophenolic Acid

Mycophenolic acid (MPA) is an immunosuppressant drug used to prevent rejection of solid organ transplants. MPA reversibly inhibits inosine monophosphate dehydrogenase (IMPDH), the rate limiting step in the biosynthesis of guanine nucleotides. The drug is marketed as the ester prodrug mycophenolate mofetil (CellCept®) for kidney, liver, and heart transplants or enteric-coated mycophenolate sodium (Myfortic®) (ECMPS) for kidney transplants. The chemical formula is $C_{17}H_{201}O_6$ and the structural formula is shown in Figure 1. The molecular mass is 320.34 $g.mol^{-1}$.

Figure 1. Structural Formula for Mycophenolate Acid



Mycophenolate mofetil comes in capsule (250 mg), tablet (500 mg), powder (200 mg/mL constituted), and intravenous (500 mg) formulations. ECMPS comes in delayed release tablets (180 mg or 360 mg). Recommended dosage regimens for adults on mycophenolate mofetil are 1 g orally twice daily for kidney transplant recipients, 1 g twice daily intravenously or 1.5 g twice daily orally for liver transplant recipients, and 1.5 g intravenously or orally for cardiac transplant recipients. Recommended dosages for adult kidney transplant recipients on ECMPS are 720 mg twice daily. In pediatric patients, recommended dosages for MMF are 600 mg/m^2 administered orally twice daily (maximum 2 g or 10 mL daily), while children with a body surface area of 1.25 to 1.5 m^2 are recommended to get 750 mg twice daily. Children with a body surface area greater than 1.5 m^2 are recommended to receive 1g twice daily.[80] Although Tacrolimus has replaced Cyclosporin A as calcineurin inhibitor comedication to a large degree, MPA was originally approved by the U.S. Food and Drug Administration only for combination with Cyclosporin. The recommended doses refer to this combination.

The pro-drug Mycophenolate mofetil is rapidly hydrolyzed to MPA by esterases in the gut, blood, liver, and kidney. ECMPS does not get hydrolyzed; it is essentially MPA in salt form. Oral bioavailability of MPA is between 81 and 94 percent after ingestion of mycophenolate mofetil and 72 percent after ingestion of ECMPS. Differences in bioavailability may be due to the fact that studies of mycophenolate mofetil were conducted on healthy volunteers while studies of ECMPS (e.g., Arns et al.[81]) were conducted on kidney transplant patients. MPA is metabolized in the liver, gastrointestinal tract, and kidney. The major metabolite, 7-*O*-MPA-glucuronide (MPAG), is inactive, and occurs in 20 to 100-fold higher concentrations than

MPA.[80] The minor acyl glucuronide metabolite AcMPAG is immunosuppressive and proinflammatory. Enterohepatic recirculation of MPA involves excretion of MPAG into bile followed by deconjugation to MPA in the gut and reabsorption into the circulation. This effect accounts for 10 to 60 percent of MPA exposure and may lead to a second peak in the MPA concentration 6 to 12 hours after dosing. Readers interested in further information on the pharmacodynamics and pharmacokinetics of MPA are referred to reviews by Staatz and Tett[80] and Bullingham et al.[82]

Solid Organ Transplant

Solid organs include the kidneys, liver, heart, lungs, pancreas, and intestines. In 2005, there were 25,737 solid organ transplants in the United States alone.[83] These transplants are used to treat end stage organ failure. One year graft survival rates range from 82.0 to 95.0 percent, due in large part to refined surgical techniques and the development of effective immunosuppressant drugs. The success of solid organ transplants has led to a situation where demand for organs far outstrips supply. In mid-2005, over 90,000 Americans were on waiting lists for solid organ transplants.[84]

Mycophenolic Acid: Use in Solid Organ Transplants

Mycophenolate mofetil. The use of mycophenolate mofetil in solid organ transplants is based on the results of five seminal, randomized controlled trials of kidney,[85-87] liver,[88] and cardiac transplant recipients.[89] In four trials, patients were randomized to receive mycophenolate mofetil or azathioprine in combination with cyclosporine and corticosteroids; one kidney trial[85] involved mycophenolate mofetil and a placebo comparison. The average duration of the trials was six to 12 months post transplant. Some data are available for 36 months post transplant.[90-92]

For the three kidney trials,[85-87] a total of 1,493 patients were randomized to treatment. Results showed benefits for 2 and 3 g daily doses of mycophenolate mofetil (MMF2, MMF3) at six months; however, benefits diminished or disappeared at 12 months and beyond. The percentage of patients with biopsy proven rejection in the placebo comparison trial[85] at six months was 17.0 percent in the MMF2 group, 13.8 percent in the MMF3 group, and 46.4 percent in the placebo group ($p \leq 0.001$). At 36 months, the difference in graft loss rates for intent-to-treat comparisons versus placebo were 7.3 percent (95 percent confidence interval [CI]: 1.1 to 14.2; $p<0.05$) for MMF2 and 3.2 percent (95 percent CI: -3.8 to 10.1; $p>0.05$) for MMF3.[90] In the two kidney trials where mycophenolate mofetil was compared to azathioprine, the primary outcome at six months was 'treatment failure' (any one of the following: biopsy proven rejection, graft loss, death, withdrawal for any reason). The percentage of patients with treatment failure in one study,[86] based in the United States, was 31.1 percent in the MMF2 group, 31.3 percent in the MMF3 group, and 47.6 percent in the azathioprine group ($p=0.021$). Percentages in the other study,[87] a multinational effort, were 38.2 percent for MMF2, 34.8 percent for MMF3, and 50.0 percent for azathioprine ($p<0.03$). The percentages of patients suffering graft loss or death at 12 months in the multinational study were 11.7 percent in the MMF2 group, 11.0 percent in the MMF3 group, and 13.6 percent in the azathioprine group ($p>0.05$). The investigators in the multinational trial reported intent to treat results at 36 months: graft and survival for patients receiving MMF2 was 81.9 percent, MMF3 was 84.8 percent, and azathioprine was 80.2 percent ($p>0.05$).[91]

In the liver study,[88] 565 patients were randomized to treatment and results favored mycophenolate mofetil after six months of followup. However, there was no difference between mycophenolate mofetil and azathioprine after one year of followup. Percentages of acute rejections and graft losses at six months were 38.5 percent in the mycophenolate mofetil group and 47.7 percent in the azathioprine group ($p<0.03$). At 12 months, percentages were 31.0 percent and 40.0 percent respectively ($p<0.06$). Graft survival at 12 months was 85.3 percent the mycophenolate mofetil group and 85.4 percent in the azathioprine group ($p>0.05$).

In the heart study,[89] primary results were reported for 578 'treated' patients who received the study medication to which they were randomized. A further 72 randomized patients withdrew from the study before initiation of treatment. At six months, 65.7 percent of mycophenolate mofetil and 73.7 percent of azathioprine patients required treatment for rejection ($p=0.026$). Mortality at 12 months was 6.2 percent in the mycophenolate mofetil group and 11.4 percent in the azathioprine group ($p=0.031$). At 36 months, 11.8 percent of the mycophenolate mofetil group and 18.3 percent of the azathioprine group died or received another transplant ($p<0.01$).[92]

Enteric-coated mycophenolate sodium. ECMPS was shown to be therapeutically equivalent to mycophenolate mofetil in two trials that were initially reported in a single publication.[1] Trial 1 contained 424 de novo kidney transplant patients and trial 2 contained 324 stable maintenance kidney transplant patients who were alive at six months post transplant. In trial 1, patients were randomized to 720 mg of oral ECMPS and placebo twice daily, or to 1,000 mg of oral mycophenolate mofetil and placebo twice daily. Placebos were disguised to look like the active drug being given in the opposing treatment arm. The primary outcome was 'treatment failure' (any one of the following: biopsy proven acute rejection, graft loss, death, or loss to followup within six months). After six months, 25.8 percent of patients in the ECMPS group and 26.2 percent in the mycophenolate mofetil group experienced a treatment failure ($p>0.05$). Failure results[93] at 12 months were 26.3 percent (ECMPS) and 28.1 percent (MMF) ($p>0.05$). Trial 2 patients were randomized to 720 mg of oral ECMPS daily or to 1,000 mg of oral MMF daily. The primary outcome was the incidence of gastrointestinal adverse events or neutropenia (less than 1,500 cells per mm^3). At three months, there was no difference in incidence of gastrointestinal adverse events (26 percent in the ECMPS group; 21 percent in the MMF group [$p>0.05$]). Nor was there a difference at six months (29 percent ECMPS; 28 percent MMF [$p>0.05$]). The authors reported the incidence of neutropenia after three months to be lower in patients receiving ECMPS (0.6 percent) versus patients receiving MMF (3.1 percent [$p>0.05$]). Neutropenia results were unchanged after 12 months of followup.[94] Concomitant therapies in both trials included cyclosporine with or without corticosteroids.

ECMPS and MMF were also compared in a single blind trial of 154 de novo heart transplant patients.[95] Results showed therapeutic equivalence between drugs. Patients were randomized to 1,080 mg ECMPS twice daily or to 1,500 mg MMF twice daily. 'Treatment failure' (biopsy proven and treated acute rejection, graft loss, or death) was the outcome. The percentage of patients having the outcome did not differ ($p>0.05$) between groups at six or 12 months of followup: 52.6 percent versus 57.9 percent at six months and 57.7 percent versus 60.5 percent at 12 months.

Adverse events. Common adverse events of MPA include gastrointestinal upset (nausea, vomiting, mild diarrhea), headache, mild weakness, dizziness or tremor, insomnia, and swelling of the lower legs or feet. There is also an increased risk of lymphoma or other cancers.[96]

In clinical trials, patients taking mycophenolate mofetil had more abdominal pain, diarrhea, esophagitis, anorexia, gastrointestinal bleeding, leucopenia, anemia, and opportunistic infections

(e.g., cytomegalovirus [CMV], herpes simplex or zoster) than patients taking placebo or azathioprine. Patients taking 3 g MMF daily generally had more adverse events than patients taking 2 g MMF daily. There were no differences in the incidence of cancers between any of the treatment groups.[85-89] In trials where mycophenolate mofetil was compared to ECMPS,[1,93,94] adverse events were generally higher in the MMF group, although the differences were not statistically significant at the 5 percent level. The incidence of gastrointestinal adverse events was higher in the ECMPS group (29.6 percent versus 24.5 percent),[94] although the difference was also not statistically significant. The incidence of cancer did not differ between treatments.

Therapeutic Drug Monitoring of Mycophenolic Acid

Therapeutic drug monitoring (TDM) is the measurement and subsequent interpretation of drug concentrations in biological fluid. Drugs exhibiting the following characteristics may warrant TDM: a good relationship between concentration and pharmacological response; wide interpatient variation in absorption, distribution, metabolism, or excretion; a narrow therapeutic range; and a pharmacological response that is not readily assessable. TDM may be useful for monitoring adherence, identifying drug interactions, and tailoring doses to specific patients.[97]

TDM has become central to the use of immunosuppressants. The aim is to improve control over acute rejection and boost the probability of long term patient and graft survival.[98] TDM of MPA is based on observed associations between total MPA area under the concentration-time curve ($AUC_{0-12\,h}$) and acute rejection in adult and pediatric patients.[11,17,42,99] However, this evidence is viewed by some as equivocal.[2,3]

Additionally, there are numerous challenges that must be addressed as a prerequisite for TDM of MPA. Most notable is the impracticality of repeated 12 hour measures of AUC in standard practice settings. There have been suggestions of methods to overcome the impracticality of total AUC (e.g., use of limited sampling strategies[4] or Bayesian estimation[2]), but none of these possibilities has been thoroughly investigated to date.

Other challenges include the difficulty of using existing, routine assays to quantitate free MPA, which is thought to be the prime driver of MPA's immunosuppressive effect, as well as the need to establish and validate effective therapeutic ranges for TDM.[4] Some researchers[3] do not believe that free MPA has much of a role in TDM because its correlation with clinical outcomes is not improved over the correlation between total MPA and clinical outcomes. Recently Roche has introduced an IMPDH based assay for free and total MPA. A CEDIA assay is now available from Microgenics.

Improved prophylaxis with multiple drugs has lowered the rejection risk. This makes additional improvements based on dosing of one drug and definition of a lower limit of the therapeutic range challenging.

Further issues in TDM of MPA include wide intra patient variability in MPA plasma concentration-time profiles, non-linear pharmacokinetics, increase of MPA exposure with time early after kidney transplantation, no established frequency and duration of monitoring, uncertainty about the extent to which baseline IMPDH may contribute to pharmacodynamic differences in persons receiving MPA, problematic bioavailability in renally impaired patients, and no agreement on a pharmacokinetic (PK) parameter that would best associate with adverse events.[4] Some[6] believe the occurrence of gastrointestinal adverse events may be associated with dose rather than a pharmacokinetic variable. Adverse events are relatively rare, not specific to

MPA, and thus difficult to assess objectively. An upper limit of a therapeutic range is therefore difficult to determine.

Scope and Purpose of the Evidence Report

This evidence report was designed and conducted to address the following key questions:

1. What is the evidence that monitoring mycophenolic acid in patients who receive a solid organ transplant results in a lower incidence of transplant rejections and adverse events compared to patients who are not monitored?

2. Does the incidence differ by any of the following?
   a) MPA dose and dose frequency;
   b) Type of MPA (mycophenolate mofetil [CellCept®], enteric-coated mycophenolate sodium [Myfortic®]).

3. a) Does the incidence differ by any of the following?
      ia. Total versus free MPA
      ib. Albumin versus MPA

      iia) MPAG, AcMPAG versus MPA
      iib) Genetic basis of differences in MPA pharmacokinetic parameters

      iii) Assay method (EMIT, HPLC, HPLC-MS, other)

   b) Does the incidence differ by analytical method of MPA monitoring?
      i. Full AUC (area under the curve)
      ii. Limited sampling strategies
         a. Predose concentrations
         b. 2h post dose concentrations
         c. Other

4. Does the evidence for monitoring MPA differ by any of the following?
   a) Age
   b) Gender
   c) Ethnicity
   d) Concomitant use of calcineurin inhibitors (e.g., tacrolimus, cyclosporine)
   e) Concomitant use of other medications
   f) Comorbidity

5. What is the short and long-term cost-effectiveness of avoiding acute rejection due to MPA monitoring?

Addressing these questions will help to gauge the strength of the evidence for TDM of MPA in solid organ transplants. As well, the exercise will identify gaps in the research and provide suggestions for future research.

Chapter 2. Methods

Analytic Framework

An analytic framework is a schematic representation of the strategy for organizing topics for review and guiding literature searches. Figure 2 illustrates the inter relationships between the key questions for this evidence report. The figure begins with the use of CellCept® or Myfortic® in solid organ transplant recipients, progresses to monitoring MPA (mycophenolic acid) concentrations in serum or plasma, and concludes with an outcome (e.g., rejection or adverse events). Throughout the entire diagram, each box is suggestive of an area where resources are consumed. The cost of these resources may be computed using standard health economics methods and compared to an outcome (e.g., life years gained, quality adjusted life years gained) to obtain incremental cost effectiveness ratios.[100]

Within the 'monitoring' subsection of the framework, the issues to consider are the form and method of MPA monitoring. In our analysis of form, we also include the type of MPA (total [bound and free], free) and the means for measuring each type in serum or plasma, namely assays such as HPLC (High-Performance Liquid Chromatography), HPLC-MS (High-Performance Liquid Chromatography-Mass Spectrometry), or EMIT (Enzyme-Multiplied Immunoassay Technique). In our analysis of form, we also include variations in albumin (to which MPA binds strongly), concentrations of MPA metabolites, and pharmacogenetics. Methods of monitoring include total AUC_{0-12} (area under the curve) and limited sampling strategies such as two hour (2h) post dose concentrations and predose concentrations.

Several factors are hypothesized to affect the utility of MPA monitoring, including age, gender, ethnicity, use of calcineurin inhibitors or concomitant medications, and comorbidity. This is because these factors may influence the disposition of MPA (i.e., adsorption, distribution, metabolism, or excretion).

Topic Assessment and Refinement

Research Team

The McMaster University Evidence-based Practice Center (MU-EPC) assembled a multidisciplinary research team with expertise in epidemiology and systematic reviews (M. Oremus, Ph.D.; P. Raina, Ph.D.), toxicology (J. Zeidler, Ph.D.), clinical chemistry (C. Balion, Ph.D.), pediatric nephrology (M. Matsuda-Abedini, M.D.), and pharmacy (M. Ensom, Pharm.D.). The team was tasked with planning an approach to completing this evidence report in a thorough, timely, and efficient manner. The team had regular meetings in the initial stages of the project to reach consensus on key methodological issues. The team was also responsible for supervising the literature search, screening, and data abstraction. The team synthesized the literature and wrote the discussion.

The research team held a 'kick-off' teleconference with representatives from the partner organization (American Association of Clinical Chemistry), the Agency for Healthcare Research and Quality (AHRQ), and MU-EPC staff at the start of the project to define the magnitude of the

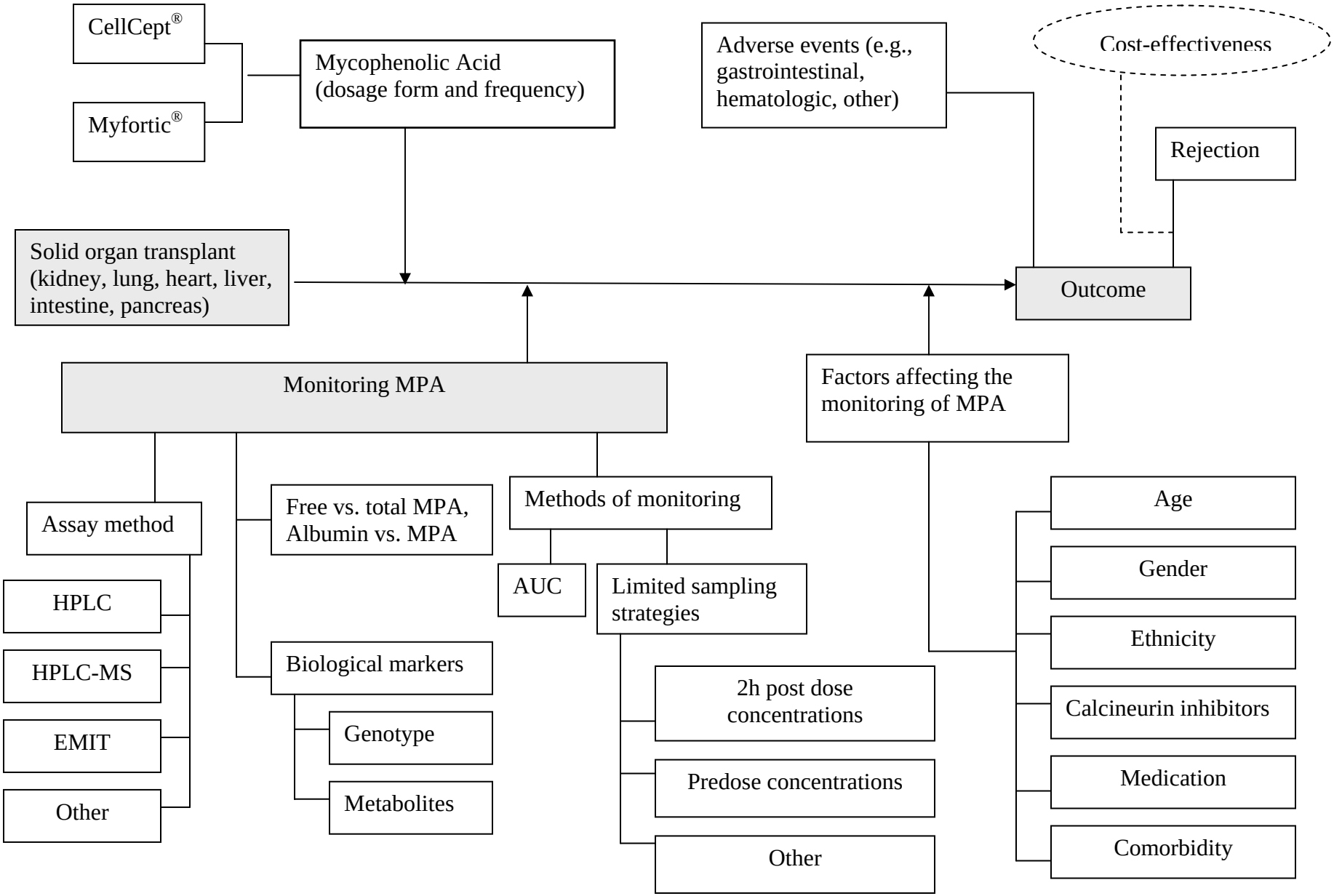
topic and refine and clarify the preliminary key questions. A Technical Expert Panel (TEP), composed of internationally recognized experts in MPA, was assembled to provide high level content expertise on MPA monitoring. Members of the TEP were requested to participate in teleconferences on an as needed basis throughout all phases of the project.

Technical Expert Panel Teleconference Calls

The first TEP teleconference call took place on February 8, 2007. Technical experts included Dr. Klemens Budde (Managing Senior Physician, University Clinic Charité), Dr. Guido Filler (Chair/Chief, Department of Pediatrics, Children's Hospital of Western Ontario), Dr. Atholl Johnston (Professor of Clinical Pharmacology, Barts and the London, Queen Mary's School of Medicine and Dentistry), and Dr. Leslie M. Shaw (Professor of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania) (see Appendix E* for a list of TEP members). A second TEP teleconference took place on April 18, 2007 (Drs. Budde, Filler, Johnston, and Shaw present). Several topics were discussed during both calls, including the definition and scope of the key questions, search strategies, inclusion and exclusion criteria, and the composition of the screening and data abstraction forms.

* Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm

Figure 2. Analytical Framework



General Methods

Key Questions

The original set of key questions for this evidence report was revised by the MU-EPC research team and discussed during the TEP teleconferences. Additional discussants at the teleconferences included representatives from the partner organization and the AHRQ's Task Order Officer (TOO).

The revised key questions are:

1. What is the evidence that monitoring mycophenolic acid in patients who receive a solid organ transplant results in a lower incidence of transplant rejections and adverse events compared to patients who are not monitored?
2. Does the incidence differ by any of the following?
   a) MPA dose and dose frequency;
   b) Type of MPA (mycophenolate mofetil [CellCept®], enteric-coated mycophenolate sodium [Myfortic®]).
3. a) Does the incidence differ by any of the following?
      ia) Total versus free MPA
      ib) Albumin versus MPA
      iia) MPAG, AcMPAG versus MPA
      iib) Genetic basis of differences in MPA pharmacokinetic parameters
      iii) Assay method (HPLC, EMIT, HPLC-MS, other)
   b) Does the incidence differ by analytical method of MPA monitoring?
      i. Full AUC
      ii. Limited sampling strategies
         a. Predose concentrations
         b. 2h post dose concentrations
         c. Other
4. Does the evidence for monitoring MPA differ by any of the following?
   a) Age
   b) Gender
   c) Ethnicity
   d) Concomitant use of calcineurin inhibitors (e.g., tacrolimus, cyclosporine)
   e) Concomitant use of other medications
   f) Comorbidity
5. What is the short- and long-term cost-effectiveness of avoiding acute rejection due to MPA monitoring?

Literature Search Strategy

We conducted a comprehensive search of the literature to capture all relevant, published studies on the topic of therapeutic drug monitoring (TDM) for MPA. The following electronic databases were searched:

1. MEDLINE® (1966- October 22, 2007);
2. BIOSIS® Previews (1976- October 22, 2007);
3. EMBASE® (1980- October 22, 2007);

4. Cochrane Database of Systematic Reviews® (1995- October 22, 2007);
5. Cochrane Central Register of Controlled Trials® (1995- October 22, 2007).

Appendix A* contains a detailed description of the database search strategies.

To supplement the database search, we examined the reference lists of several recently published review articles[3-6] and consulted with the TEP to identify additional published studies.

Inclusion/exclusion criteria. We included studies published in the English language, provided they were randomized controlled trials (RCTs), observational studies with comparison groups (e.g., cohort, case control), or case series (a retrospective or prospective study with a single group of subjects [no comparison group] enrolled according to predefined criteria). Case reports, narrative and systematic reviews, editorials, comments, letters, opinion pieces, abstracts, conference proceedings, and animal experiments were excluded from the report. We included studies of pediatric and adult patients who received allograft solid organ transplants from live or deceased donors, provided that any form of MPA was measured in serum or plasma. At least one measure, at one point in time, had to be made using any method of measurement (e.g., AUC). We excluded studies that did not link the measures of MPA in blood to a health outcome. Examples of health outcomes included transplant rejection, graft survival, overall patient survival, or mortality. Certain biomarkers (e.g., serum creatinine, glomular filtration rate [GFR]) and all adverse events were also considered health outcomes.

Data Collection and Reliability of Study Selection

A team of trained raters, composed of research assistants, MU-EPC staff, and members of the research team, applied the inclusion and exclusion criteria to the citations that were identified in the literature search (see Appendix B). A guide and standardized forms were developed to govern the screening process. The forms were created and stored online using Systematic Review Software v4.0 (SRS; TrialStat Corp., Ottawa, Ontario, Canada).

The screening process was divided into two levels: title and abstract, and full text. For title and abstract screening, two independent raters evaluated the citations that were obtained from the literature search. Citations that met the inclusion criteria or for which there was insufficient information to determine whether or not they did, were retrieved for further assessment. Once retrieved, the entire study publication (full text) was screened to determine if the inclusion criteria were met. At this stage, the raters assigned the included studies to categories based on the key question or questions to which the studies applied. Inclusion of studies required agreement from both raters. Discrepancies were resolved by consensus. If consensus could not be reached, then a third party arbitrator reviewed the study in question and made a final decision. The arbitrator was an epidemiology trained member of the MU-EPC staff who was not otherwise involved in the screening process.

Studies that passed the full text screening phase proceeded to full data abstraction. Data were abstracted by MU-EPC staff (including two trained physicians). Members of the research team who were responsible for synthesizing data for the key questions reviewed the abstractions to confirm the accuracy of the work.

* Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm

Quality Assessment of Included Studies

The methodological quality of included studies was assessed using 'core' criteria enumerated in the draft Evidence-based Practice Center Methods Manual (under preparation by the AHRQ). These core criteria represent the most important elements by which to judge study quality.[101,102] The criteria were formulated into questions, which are shown in Appendix B[*]. Two reviewers independently assessed study quality and resolved discrepancies by consensus.

For controlled trials, we examined the following topics: method of randomization, method of allocation concealment, baseline comparison of groups, differences between groups at baseline, availability of intent to treat analysis, description of methods used to measure MPA, definition of the outcomes related to monitoring MPA, blinding of subjects, persons measuring MPA, persons assessing outcomes and the presence of a differential loss to followup between groups.

For observational studies, we examined the following topics: sample size for primary and secondary outcomes, selection method of subjects, baseline comparison of groups, differences between groups at baseline, description of the methods used to measure MPA, definition of outcomes related to monitoring MPA, blinding of subjects, persons measuring MPA, persons assessing outcomes, presence of a differential loss to followup between groups and whether the authors controlled for confounding.

Summary of Findings: Descriptive and Analytic Approaches

A qualitative descriptive approach was used to summarize study characteristics and outcomes. Multiple reports on the same study cohort were grouped together and treated as a single study with the most current data reported for presentation of summary results.

Descriptive approaches were used to summarize the characteristics of included studies and answer the key questions. The research team judged that a meta-analysis was not feasible because the included studies contained far too much clinical and methodological heterogeneity. Instead, data were collected during the abstraction on the characteristics of study participants, treatment regimen, form of MPA, method of measuring MPA, measurement time points, and outcomes. The quality of this information was judged and the findings were summarized in both text and tables. This evidence report provides a greater understanding of TDM for MPA, identifies gaps in existing research, and suggests future research.

Peer Review Process

The partner organization, TOO, research team, and members of the TEP identified potential peer reviewers. The MU-EPC compiled a list of these reviewers, all of whom were approved by the AHRQ prior to the circulation of the draft report. The reviewers were asked to review the report and provide feedback on clinical and methodological content, as well as on the readability and presentation of information. Their comments and suggestions were incorporated where possible.

[*] Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm

Chapter 3. Results

Literature Review and Screening

The literature search yielded 11,642 citations. In total, 1,147 citations (96 percent) were excluded from further review following initial title and abstract screening; 495 citations proceeded to full text screening. Of these 495 citations, 406 (82 percent) were excluded from further review and 89 (18 percent) advanced to the data abstraction phase. At this phase, the 89 studies were slotted according to the key question or questions to which they applied. Three studies[103-105] were not relevant for any of the review questions. Figure 3 depicts the flow of studies through the screening process. As well, the figure shows the reasons for study exclusion. The remainder of this chapter contains sections describing the evidence for the key questions and a quality assessment of the studies.

Key Questions

Question 1. What is the Evidence That Monitoring Mycophenolic Acid in Patients who Receive a Solid Organ Transplant Results in a Lower Incidence of Transplant Rejections and Adverse events Compared to Patients who are not Monitored?

Only three studies (four reports)[7-10] contained one group of patients who were monitored and one group of patients who were not monitored. The first study was published by Meiser et al. in two companion papers with identical results.[7,8] The investigators consecutively enrolled 15 adult, orthotopic heart transplant patients into a study of fixed dose MMF (Mycophenolate Mofetil) (2 g daily) and tacrolimus (group 1). A further 30 patients with the same characteristics were subsequently enrolled to receive MMF and tacrolimus, with MMF dose adjusted according to plasma predose concentration (group 2). Target plasma predose concentrations were set within a range of 2.5 to 4.5 μg/mL. Mean lengths of followup were 696 days (group 1) and 436 days (group 2). Five group 1 patients remained rejection free over the course of followup; 27 group 2 patients also remained rejection free. Plasma MPA (Mycophenolic Acid) predose concentrations were measured retrospectively in group 1 patients and an inverse association was found between mean plasma MPA and the number of rejection episodes per patient: 0 rejections (3.6 μg/mL); one to two rejections (2.2 μg/mL); three rejections (1.4 μg/mL). For group 2 patients, the authors report only the MPA plasma concentrations for the three patients who suffered rejection (1 rejection episode per patient): 0.7, 1.3, and 0.9 μg/mL. Diarrhea or vomiting were reported in six group 1 patients and nine group 2 patients; cytomegalovirus (CMV) was reported in three group 1 patients and four group 2 patients. The authors do not provide p-values or confidence intervals for any inter or intra-group comparisons.

Flechner et al.[9] conducted a similar sequential allocation study by recruiting one group (n=160) of kidney transplant recipients who received a fixed dose of 2 g MMF daily and a starting dose of 5 g p.o. sirolimus. After this group was recruited, the investigators recruited another group (n=100) who received 1 g MMF daily (sirolimus regimen unchanged relative to

2 g group). Dosage in the 1 g group was adjusted to keep MPA C_0 concentrations between 1.8 and 4.0 μg/mL.

After six months of followup, there were no differences ($p>0.05$) between groups in biopsy confirmed acute rejections (8.8 percent [2 g] versus 13.0 percent [1 g]) or mean serum creatinine concentrations (1.41 mg/dL [2 g] versus 1.47 mg/dL [1 g]). There were also no differences in the incidence of CMV or Polyoma viral infections. However, the incidence of some gastrointestinal adverse events was lower in the 1 g group: nausea, vomiting, or dyspepsia (8.0 percent versus 20.6 percent; $p=0.007$); abdominal pain (4.0 percent versus 10.6 percent; $p=0.05$); diarrhea (20.0 percent versus 34.3 percent; $p=0.01$).

The third study,[10] which was published online in October 2007, was a 12 month RCT comparing adult kidney transplant patients in France. Patients received a quadruple immunosuppressive regime that included randomization to fixed-dose or concentration-controlled MMF. Persons in both groups received 2 g MMF daily for seven days, after which the fixed-dose group could receive dose adjustments based on physician experience. In the concentration-controlled group, a three-point, limited AUC (area under the curve) sampling strategy (20, 60, and 180 minutes post-MMF administration) was calculated using Bayesian estimates to achieve an MPA target dose of 40 mg h/L. MPA was measured with the HPLC assay at days 7 and 14 post-transplant, as well as at months 1, 3, 6, and 12. The primary endpoint was treatment failure, which was a composite endpoint consisting of death, graft loss, acute rejection (renal biopsy or Banff classification), or MMF discontinuation. The primary analysis was an intent-to-treat analysis consisting of 65 patients in each group. There were more treatment failures in the fixed-dose group (n=31; 47.7 percent) than in the concentration-controlled group (n=19; 29.2 percent) ($p=0.03$). The principal component of these failures was the difference in any type of acute rejection (fixed-dose: n=20 rejections; concentration-controlled: n=8 rejections [$p=0.01$]). The remaining components of the composite outcome were not statistically significantly different at the 5 percent level. Adverse events tended to be higher in the concentration-controlled group, although the only statistically significant difference ($p<0.05$) was observed in the case of herpes (eight events in the concentration-controlled group; one event in the fixed-dose group).

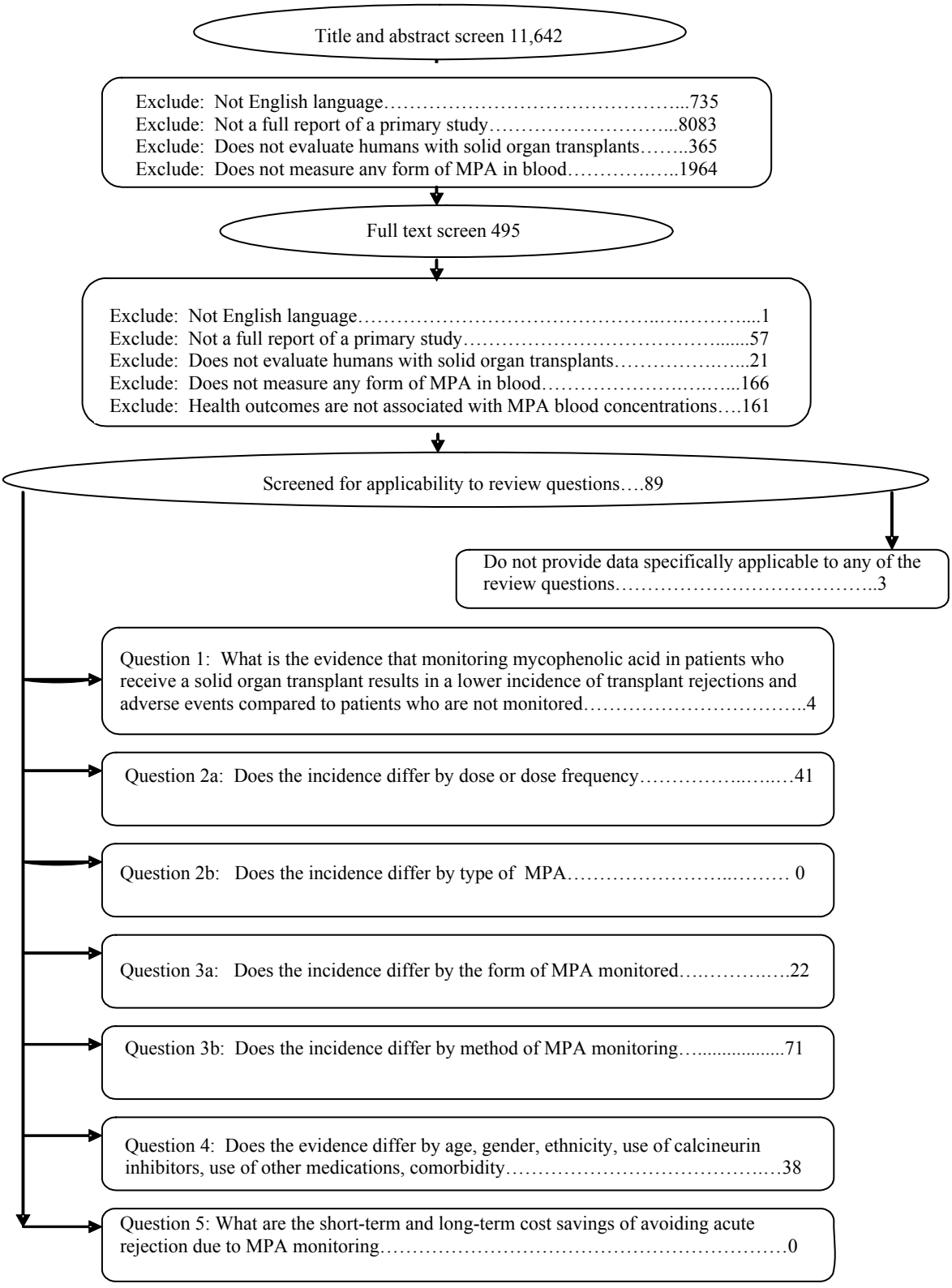


Figure 3. Flow diagram showing the number of citations processed at each level of the screening process

Question 2. Does the Incidence Differ by any of the Following?

2a: MPA Dose and Dose Frequency

The association between dosage and incidence of transplant rejections and adverse events has been described in 41 articles (38 separate studies) of patients who received a solid organ transplant (See Evidence Table 1, Appendix C*).[7,8,11,12,14-16,18,21,22,24,25,27,28,30,31,33,35,36,39-42,44,51-53,56,59-62,67,69,72,73,75-77,106,107] Of the 41 articles, one[7] was described in a duplicate report,[8] two others reported on the same study (i.e., study design and patient population) yet contained different analyses,[11,12] and another study reported with two different analyses.[36,52] Five studies (six articles) were randomized controlled trials,[11,12,25,28,51,75] two (three articles) were non randomized controlled trials,[7,8,31] seven (one of which was also described in a separate case series) were prospective cohort studies,[24,35,39-41,52,77] two were case control,[53,106] two were retrospective cohort studies,[22,42] and 20 (one of which was already described in a separate prospective cohort study[52]) were case series.[14-16,18,21,27,30,33,36,44,56,59-62,67,69,72,73,76]

Most studies were in kidney transplant recipients. Liver transplant recipients were studied separately in three studies,[40,61,62] with kidney transplant recipients in one study,[39] and kidney and small bowel transplant recipients in another.[24] Heart transplant recipients were studied in five studies (six reports).[7,8,42,44,45,70] Pediatric transplant recipients were studied separately in two studies,[27,73] with young adults in one study,[44] and adults in one study.[40] Of the four pediatric studies, two were kidney transplant,[27,73] one was liver transplant,[40] and one heart transplant.[44] Young adults were studied with adults in one kidney transplant study.[41] All other studies involved persons over 16 years of age. There were no studies comparing dose frequencies.

The results of the studies for Question 2a are shown in Tables 1 to 4. In the following paragraphs, we outline the results of the most important studies that address this issue. A total of 10 studies[11,28,30,31,33,35,36,42,52,53] examined whether MMF dosage was associated with rejection. Three studies[30,31,35] found an association and seven did not.[11,28,33,36,42,52,53] Only one study, an RCT by Hale et al.,[11] attempted to compare rejection outcomes for subjects with planned dose adjustments based on different target MPA plasma or serum concentrations.

In the Hale et al. trial kidney transplant recipients were allocated to three pre-defined MPA AUC groups (low: 16.1 µg h/L; intermediate: 32.2 µg h/L; high: 60.6 µg h/L). The incidence of biopsy proven acute rejection was 25.5 percent, 8.5 percent, and 5.8 percent respectively in each of the three groups (p=0.043). Univariate logistic regression p-values between biopsy proven rejection vs. MPA AUC_{0-12}, MPA C_{max}, MPA C_0, and MMF dose were < 0.0001, 0.0008, 0.0049, and 0.0918, respectively (not significant for MMF dose). In multivariable logistic regression analysis, MPA AUC remained statistically significant, but MPA C_{max}, MPA C_0 (predose plasma or serum concentration), and MMF dose were all not significant.

There were a total of 20 studies containing evidence about whether MMF dosage was associated with adverse events. Ten (11 reports) showed statistically significant associations[11,12,14-16,22,33,62,69,72,75] and 10 showed no significant associations.[14,21,31,35,51,53,56,61,72,76] Positive associations were observed in the RCT conducted by Hale et al.[11] and van Gelder et al.[12] (two reports using data from the same trial), which was the only study that attempted to compare adverse effect outcomes for subjects with planned dose adjustments based on different target MPA plasma concentrations (low: 16.1 µg h/L; intermediate: 32.2 µg h/L; high: 60.6 µg h/L).

* Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm

The risk of diarrhea and the risk of premature study withdrawal due to adverse events were both significantly associated with mean MMF dose.[11] Posthoc analysis further showed that only the premature withdrawal due to gastrointestinal (and not other) adverse events was significantly related to MMF dose. This suggests that high local, non systemic, drug concentrations may be responsible for MMF's gastrointestinal adverse events. A case series conducted by Hubner et al.[56] in kidney transplant recipients reported adverse events for subjects with planned dose adjustments based on MPA predose concentrations and subjects taking MMF without changes based on plasma concentrations. The data were graphically depicted and, as such, no direct comparisons could be made. However, the data did show that there was no significant difference in mean MMF dose between patients with or without adverse events (1.77 g/day versus 1.89 g/day, $p>0.05$).

2b: Type of MPA (mycophenolate mofetil [CellCept®], enteric-coated mycophenolate sodium [Myfortic®])

There was no evidence in the included studies to answer this question. ECMPS was used in only one study,[32] which consisted of 12 kidney transplant recipients who were given 720 mg of the drug twice daily within 48 hours post transplant. All of the other included studies used MMF. No study contained direct comparisons of ECMPS and MMF.

Question 3a: Does the incidence differ by any of the following?

Does the Incidence Differ by Albumin versus MPA?

Twenty two studies included measurements of free MPA or albumin in addition to total MPA (See Evidence Table 1, Appendix C*).[13-21,38,40,52,53,66,69,79,108-113] There were 12 case series,[14-19,21,66,69,110,111,113] six prospective cohort studies,[13,20,38,40,52,79] two case control studies,[53,112] and two non randomized controlled trials.[38,108] The transplanted organs were livers in two studies,[40,66] hearts in one study,[19] and kidneys in the remaining 19 studies. Sample sizes ranged from eight[21,113] to 210.[40] Patients were between 0.3[40] and 77 years old.[38] The percentage of male study subjects ranged from a low of 38 percent in one study[21] to a high of 82 percent in another.[19] Patients were followed up from one[111,113] to 38 months.[14] Of these 22 studies, 13 compared total with free MPA or albumin.[13-21,109,110,112,113] Out of these, the eight studies most relevant to Question 3aia associated adverse events or rejection with measurements of free vs. total MPA[13,15-20] or albumin versus total MPA.[14] See Table 5. All studies except Maes et al.[16] and Shaw et al.[20] analyzed rejection outcomes. Rejection of a kidney was biopsy proven whenever possible and scored according to Banff criteria in four studies.[13-15,17] Kidney rejection was not defined by Cattaneo et al.[18] Rejection of a heart was determined by endomyocardial biopsy according to International Society for Heart and Lung Transplantation criteria.[19] Maes et al.[16] looked at orocecal transit time (OCTT) and oroanal transit time (OAT) as measures of motility and intestinal absorption in renal transplant patients with persistent afebrile diarrhea. Kidney function tests were analyzed in relation to MPA PK (pharmacokinetic) parameters in six studies.[13-15,17,18,20]

* Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm

All studies except DeNofrio et al.[19] had adverse events as outcomes. Adverse events (gastrointestinal, haematological, infectious) were well defined by Borrows et al.,[14] Atcheson et al.,[13] and Weber et al.[17] Gastrointestinal and haematological adverse events were well defined by Kuypers et al.[15] and Cattaneo et al.[18] Shaw et al.[20] had clear definitions of haematological adverse events, but not gastrointestinal adverse events. Albumin in relation to MPA PK parameters was analyzed in five studies.[13,14,17,18,20] In addition to the eight most relevant studies, five studies compared free and total MPA in relation to kidney function tests or albumin, but not to adverse events or rejection.[21,109,110,112,113]

The remaining nine studies were not directly relevant to the key question. Eight studies related total, but not free MPA or albumin, to an outcome.[40,52,53,66,69,79,108,111] Another study related free MPA to albumin and renal function and total MPA to adverse events and rejection.[38]

Rejection, adverse events, and free versus total MPA. Nine studies associated free MPA PK parameters or albumin with adverse events or rejection.[13-21] Four of these studies did not find statistically significant associations between free MPA parameters and adverse events or rejection, nor differences in this respect between free and total MPA.[15,19-21] Kuypers et al.[15] did not find significant associations between free or total MPA C_0, C_{max} (maximum concentration), or AUC values and rejection or adverse events in inter and intra-patient comparisons (data not shown by authors; p-values only given as not significant). Free median MPA predose concentrations within 19 patients were 27.9 µg/L without anemia and 34.2 µg/L with anemia; total MPA predose concentrations were and 2.61 mg/L without and 2.0 mg/L with anemia. DeNofrio et al.'s study[19] of heart transplant patients found lower AUCs of total MPA and free MPA (fMPA) in grade 2/3 rejection versus grade 0 or grade 1 rejection (all results significant except the total MPA grade 2/3 versus grade 0 comparison [$p<0.08$]). However, there were no reported differences for free versus total MPA. Two studies found that five[20] or four[21] patients with impaired renal function who developed leukopenia tended to have higher fMPA AUCs than patients who did not develop leukopenia, but the small numbers did not allow statistical conclusions. No comparison to total MPA was made in these cases. Diarrhea in 10 out of 33 patients was not associated with high free or total MPA C_0 or predose values (data not shown by authors).[20]

Atcheson et al.[13] found no association between free or total MPA parameters and rejection, gastrointestinal effects, or anemia. On the other hand, the mean fMPA AUC_{0-6} was significantly higher in patients with thrombocytopenia, leucopenia, or infections (1.9 mg h^{-1} l^{-1}) than in patients without these outcomes (1.1 mg h^{-1} l^{-1}; 95 percent CI for the difference: 0.3 to 1.4; $p=0.0043$). Total MPA AUC_{0-6} values for these outcomes were not different ($p=0.18$). Weber et al.[17] also found that fMPA AUC, but not total MPA AUC, were associated with leukopenia and infections. Similarly, Cattaneo et al.[18] saw a correlation between the free fraction of MPA (but not total MPA) and lower red blood cell and leukocyte counts. Borrows et al.[14] did not measure fMPA, but correlated hypoalbuminemia and renal impairment, both known to increase fMPA (see below), with hemotoxicity. Multivariable analysis showed that higher MPA predose concentrations, lower serum albumin, and lower estimated creatinine clearance (eCrCl) were independently associated with a higher probability of anemia (relative risk [RR] for 1 mg/L rise in median MPA concentration in the 30 days before the event: 1.62; 95 percent CI: 1.24 to 2.12; RR for 10 g/L rise in albumin: 0.70; 95 percent CI: 0.40 to 0.87; RR for 10 mL/min rise in eCrCl (estimated creatinine clearance): 0.80; 95 percent CI: 0.67 to 0.91; $p<0.001$ for all). According to receiver operating curve (ROC) analysis, an MPA predose concentration of 2.60 mg/L and a serum albumin concentration of 29 g/L best discriminated patients with and without anemia.

Maes et al.[16] studied patients with unexplained enterocolitis and persistent afebrile diarrhea without evidence of infections and found a correlation between oroanal transit time and MPA (r=-0.87; p=0.02) or fMPA (r=-0.88; p=0.02), but no difference between MPA and fMPA (p>0.05). They hypothesized MPA to be causal in this relationship. None of the studies above seemed to have found free MPA PK parameters useful to predict diarrhea or rejection.

Kidney function, albumin, and free MPA. Studies that related kidney function or albumin to free MPA measurements[13,15,20,21,38,109,110,112,113] generally found that impaired kidney function as well as hypoalbuminemia were associated with increased concentrations or AUCs of fMPA and MPAG but not total MPA. Weber et al.[112] showed that free, but not total, MPA AUC_{0-12} values were inversely correlated with GFR (Glomerular Filtration Rate) in 18 children and 10 adults (r=- 0.57, $p < 0.01$ at 1 week; r=-0.41, $p < 0.05$ at 3 weeks after renal transplantation). In children (36 observations from weeks 1 and 3 combined), the MPA free fraction was inversely correlated with serum albumin (r=-0.54, p<0.01) and GFR (r=-0.60, p<0.001). Forward stepwise regression showed that the free fraction of MPA was significantly related to albumin and GFR (r^2=0.46). In adults the MPA free fraction was also inversely correlated with GFR (r=-0.70, p<0.005), but not with albumin. Conversely, Johnson et al.,[111] who did not measure fMPA, found by multiple linear regression in 10 kidney transplant patients that creatinine (p=0.01) and albumin (p=0.03) predicted total MPA AUC_{0-12}.

Does the Incidence Differ by Genetic Differences or Metabolite Concentrations?

The relationships between genetic polymorphisms, pharmacokinetics of MPA, and health outcomes were examined by two studies.[30,79] Twenty three studies reported measurement of the major, inactive, phenolic conjugate metabolite mycophenolic acid-7-O-glucuronide (MPAG) (See Evidence Table 1, Appendix C* and Table 6).[15,16,18,20-25,32,38,44,58,64,73,108-115] The active acyl glucuronide metabolite of MPA (AcMPAG) was measured in two of the 23 studies.[15,16] Fourteen studies were case series,[15,16,18,21,30,32,44,58,64,73,110,111,113,116] six were prospective cohort studies,[20,23,24,79,109,115] two were non randomized controlled trials,[38,108] one was a retrospective cohort study,[22] one was a case control study,[112] and one was a randomized controlled trial.[25] Almost all studies dealt only with kidney transplantation, except for two heart transplant studies[44,58] and one study including liver, small bowel, and kidney recipients.[24] Samples ranged from five[115,116] to 95 people.[79] Ages ranged from 1 month[44] to 77 years.[38] Between 20[115,116] and 73 percent[38,58] of participants were male and were followed up from 2 days[115,116] to 3 years.[23]

Outcomes described in one of the genetic papers[79] included diarrhea, leucopenia, and other haematological disorders, as well as biopsy proven acute rejection, all in relation to single nucleotide polymorphisms (SNPs). Liver dysfunction was also described in relation to MPA PK parameters and SNP genotype.[79] Delayed graft function and hypoalbuminemia were associated with MPA PK parameters. The second genetic study[30] associated MPA PK parameters and SNPs with acute rejection (classified according to Banff criteria) and diarrhea (undefined) with genotype.

Sixteen out of the 23 studies that measured metabolites compared PK parameters of MPA with those of its metabolites in relation to health outcomes.[15,16,20-25,38,108,110-115] Out of these studies, the seven studies most relevant to questions about biological variation associated adverse

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events or rejection with measurements of MPA versus metabolites.[15,16,20,22-25] Adverse events were described by five studies[15,20,22,23,25] Merkel et al.[22] list hemoglobin, elevated transaminases, CMV infection, and diarrhea (all undefined) as adverse drug reactions. Kuypers et al.[15] reported anemia (hemoglobin < 11 g/dL beyond the first month), leukopenia (white cells < 4 x 109/L) and other less well defined adverse events. Maes et al.[16] reported fecal fat loss and Bunchman[23] reported undefined gastrointestinal, haematological, and infectious adverse events. Tsaroucha et al.[24] described only minor gastrointestinal problems without attempts at correlation to MPA. Shaw et al.[20] defined leukopenia (whole blood count < 5000), but not gastrointestinal effects. Behrend et al.[25] did not specify their observed adverse events. A few studies[22,25,117] did not contain clear definitions of rejections. Others[15,16,23] used Banff criteria if biopsy was not contraindicated. Shaw et al.[20] defined rejection as based mostly on creatinine, but didn't relate this outcome to MPA or metabolites, and neither did Maes et al.[16] Renal function tests or albumin were evaluated in connection with MPA or metabolites in four of the seven studies.[15,20,22,25] The seven studies of highest relevance were accompanied by nine studies that compared MPA and metabolites related to lab based outcomes, but not to adverse events or rejection.[21,108-113,115,116]

The remaining seven less relevant studies did not compare either MPA to metabolites or associate outcomes with metabolites.[18,32,38,44,58,64,73] They did relate MPA mostly to rejection outcomes.

Pharmacogenetics. Naesens et al.[79] found that seven days after transplantation, renal allograft recipients (n=9) without the C-24T SNP of the multidrug resistance associated protein 2 (MRP2), but with mild liver dysfunction, had lower MPA exposure compared to MRP2 C-24T non carriers (n=45) without liver dysfunction. Dose corrected MPA C_0 concentrations were 1.9 ± 1.6 versus 3.8 ± 3.2 mg/L·g (p=0.045) in liver disease versus no liver disease. Dose corrected MPA AUC_{0-12} values were 34.1 ± 16.8 versus 81.8 ± 51.0 mg·h/L·g (p=0.0007). MPA exposure in carriers of the MRP2 C-24T variant were similar with (n=7) or without (n=34) liver dysfunction. In this subgroup, the dose corrected MPA C_0 concentrations were 3.4 ± 2.5 versus 4.0 ± 2.5 mg/L·g (p > 0.05) in liver disease versus no liver disease. Dose corrected MPA AUC_{0-12} values were 94.4 ± 50.4 versus 79.6 ± 35.4 mg·h/L·g (p=0.0007). The C-3972T variant, in linkage disequilibrium with C-24T, led to similar effects. The C-24T SNP was associated with higher MPA exposure later after transplantation and with more diarrhea within one year after surgery.

Satoh et al.[30] studied the circadian variation of MPA PK, the association between MPA PK and acute rejection, and the association of several polymorphisms related to the Clock gene, the uridine diphosphoglucuronosyltransferase (UGT) system, cytochrome P450 3A5, and the multidrug resistance 1 (MDR1) C3435T variant, with circadian MPA variation and the incidence of adverse events and rejection. MPA PK was found to vary with the time of the day (daytime AUC > nighttime AUC). MPA PK parameters were lower in patients with acute rejection than in those without, and the MDR1 C3435T genotype was associated with a higher incidence of diarrhea than in patients with the CC genotype (p=0.049). No direct associations between genotype, MPA PK, and outcomes were found.

Rejection, adverse events, and metabolites versus MPA. Seven studies related adverse events or rejection with measurements of MPA versus metabolites.[15,16,20,22-25] Significant associations were found in two studies.[15,16] Kuypers et al.[15] reported higher median AcMPAG (0.24 versus 0.12 mg/L, p=0.03), MPAG C_0 concentrations (62.8 versus 58.3 mg/L, p=0.02), and AcMPAG/MPA ratios (0.10 vs. 0.06, p=0.004), but not higher MPA C_0 concentrations (2.0 vs.

2.61 mg/L, p>0.05) in patients who experienced anemia compared with times when they did not experience anemia (intra-patient comparison, 19 concentrations). The authors also found lower median MPAG C_0 concentrations (n=10) at times of a leucopenia episode compared to concentrations at times of no leukopenia (47.2 versus 60.5 mg/L, p=0.04). With these exceptions, inter- and intra-patient comparisons of C_0 concentrations, AUCs, or C_{max} concentrations of MPA, fMPA, AcMPAG, and MPAG between the presence or absence of acute rejection, diarrhea, leucopenia, and anemia yielded no significant differences.

Maes et al.[16] found a correlation between the amount of fecal fat loss (a measure of fat malabsorption with steatorrhea) and MPAG concentrations (r=0.9955, p<0.001), as well as AcMPAG concentrations (r=0.90, p=0.015) in five renal allograft recipients with persistent afebrile diarrhea.

Negative results concerning MPA and MPAG concentrations were found in association with the following: elevated transaminases, CMV infections, diarrhea, and rejections;[22] diarrhea, anemia, leucopenia, sepsis, and rejections (no data shown);[23] adverse gastrointestinal effects and rejection in liver transplant recipients;[24] diarrhea;[20] and unnamed adverse events and rejection (data not shown).[25]

Kidney function, albumin and metabolites versus MPA. Thirteen studies compared MPA and metabolites related to lab based outcomes.[15,20-22,25,108-113,115,116] MPAG C_0 concentrations or AUCs were found in all these studies to significantly increase with decreased kidney function as measured by creatinine concentrations or clearance. MPA C_0 and AUC results behaved less predictably and could either increase, decrease, or not change with kidney function. In a study of kidney transplant recipients,[109] MPAG C_0 and AUC were elevated in renal insufficiency compared to preserved renal function (MPAG C_0 = 274 ± 114 versus 92.6 ± 36 ug/mL, p<0.001; MPAG AUC = 3527 ± 1130 versus 1550 ± 392 µg·h/mL, p < 0.001). In contrast, MPA C_0 was elevated (2.12 ± 1.4 versus 1.15 ± 0.6 µg/mL, p=0.037), but MPA AUC was not (48.9 ± 19 versus 47.3 ± 8.8 µg·h/mL, p > 0.05).

Albumin was correlated to MPA, but not to MPAG.[22,111] Multiple linear regression with adjustment for covariates found that serum albumin in renal allograft recipients positively predicted MPA AUC_{0-12} (p=0.03), but not MPAG AUC_{0-12}.[111]

Does the Incidence Differ by Assay Method?

Among all the included studies, only two case series[26,27] involved direct comparisons of different assay methods (See Evidence Table 1, Appendix C*). Both case series contained children with transplanted kidneys from the same longitudinal research project.[17,110,112,118] In one study, by Weber et al.,[26] 50 patients (31 males) were between 3.2 and 16.0 years old. In the other study, by Armstrong et al.,[27] the authors did not report the age or sex of their subgroup of 40 patients. Followup was for six months[26] or 70 days.[27]

Both papers reported the EMIT (Enzyme multiplied immunoassay technique) and HPLC (High performance liquid chromatography) assays to measure total MPA C_0, C_{max}, and AUC_{0-12}. Weber et al.[26] also measured C_{12} (evening predose) and two abbreviated AUCs. Fifteen of the patients in the Weber et al. study had a rejection, 11 of which were biopsy proven (Banff criteria) and four of which were diagnosed on the basis of one or more clinical findings (i.e., body temperature, graft swelling, tenderness, creatinine 20 percent more than baseline value, oliguria).

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Nine patients in the Armstrong et al. study had acute rejection, which the authors did not define.[27]

Both studies found EMIT and HPLC equally able to discriminate between patients with acute rejections during the first 70 days post transplant. This was true for C_0 and AUC_{0-12} in the Armstrong et al. study[27] and for C_0, C_{12}, AUC_{0-12} and the abbreviated AUC estimate $AUC_{0,75min,4h}$ in Weber et al.[26] Decision concentrations, below which the risk of acute rejection is increased, were higher with EMIT than with HPLC, presumably because of the known cross reactivity of the EMIT assay with the active metabolite AcMPAG.[119] The cut offs for AUC_{0-12}, with a diagnostic sensitivity of 67.7 percent and a diagnostic specificity of 79.4 percent, were 29.5 mg·h/L for HPLC and 36.1 mg·h/L for EMIT.[27] The other study showed AUC_{0-12} cut offs at 80 percent sensitivity and 57 percent specificity to be 33.8 mg·h/L (HPLC) and 36.1 mg·h/L (EMIT).[26] Cut offs for C_0 were 1 mg/L (sensitivity 77.8 percent, specificity 64.5 percent, HPLC) and 1.3 mg/L (EMIT).[27] Weber et al.[26] reported a better performance of C_{12} versus C_0 with cut offs for C_{12} of 1.2 (HPLC) and 1.4 mg/L (EMIT) (sensitivity 80 percent, specificity 60 percent). Areas under the ROC curves for C_0, C_{12} and AUC_{0-12} ranged from 0.64 (EMIT, AUC, 95 percent confidence interval (CI): 0.45 to 0.84; p=0.04) to 0.70 (HPLC, C_{12}, 95 percent CI: 0.53 to 0.87; p=0.01),[26] or from 0.71 (EMIT, 95 percent CI: 0.51 to 0.91; p=0.020 [AUC]; 0.53 to 0.89; p=0.012 [C_0]) to 0.73 (HPLC, AUC, 95 percent CI: 0.53 to 0.94; p=0.012).[27] C_{max} was not able to discriminate rejectors significantly in either study. None of the PK parameters, regardless of assay method, were associated with the incidence of adverse events (diarrhea, anemia, thrombocytopenia, leukopenia, and several viral, fungal and bacterial infections).[26]

HPLC-MS was used so rarely that the performance of this assay method could not be assessed.

3b: Does the Incidence Differ by Method of MPA Monitoring (Full AUC or Limited Sampling Strategies [i.e., Predose Concentrations, 2 hour Post Dose Concentrations, Other])?

The association between the method of MPA monitoring and incidence of transplant rejections and adverse events has been described in 71 reports (67 separate studies) of patients who received a solid organ transplant. The characteristics of these studies are shown in Evidence Table 1, Appendix C*).[7,8,10-22,24-77,106,120] Of the 67 studies, one[7] was described in a duplicate report,[8] another was first described partially[120] and then in full,[48] two other articles reported on the same study (study design and patient population) yet involved different analyses,[11,12] and another study reported with two different analyses.[36,52] Eleven studies (12 articles) were RCTs,[10-12,25,28,29,34,50,51,65,68,75] four (five articles) were non randomized controlled trials,[7,8,31,38,49] nine (one of which was also described in a separate case series) were prospective cohort studies,[13,20,24,35,39-41,52,77] three were case control,[53,54,106] three were retrospective cohort studies,[22,42,55] and 41 (including one[48] that was also published partially[120]) were case series.[14-19,21,26,27,30,32,33,36,37,43-48,53,54,56-64,66,67,69-74,76,106]

Most studies were in kidney transplant recipients. Liver transplant recipients were studied separately in six studies,[34,40,61,62,66,71] with kidney transplant recipients in one study,[39] and with kidney and small bowel transplant recipients in one study.[24] Heart transplant recipients were studied in eight studies, (nine reports).[7,8,19,42,44,45,55,58,121] Pediatric transplant recipients were

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studied separately in seven studies,[17,26,27,46,55,63,73] with young adults in one study,[44] and with adults in one study.[40] Of the nine pediatric studies, all involved kidney transplant with the exception of one in liver transplant[40] and two in heart transplant.[44,55] Young adults were studied with adults in one kidney transplant study.[41] All other studies involved persons older than 16 years of age.

Of the RCTs, only one is a head-to-head study of concentration monitoring versus no concentration monitoring[10] and only two trials (three articles)[11,12,29] had the primary aim of correlating pharmacokinetic parameters with clinical outcomes. None of the other RCTs were designed with this aim in mind and hence they did not provide direct evidence of the utility of MPA measurements as they related to clinical outcomes.

Method of MPA Monitoring. MPA monitoring took the form of full AUC measurements over a 12 hour period (AUC_{0-12} – seven to 10 plasma or serum samples) in 17 reports.[11,12,17,26-30,32,33,35,36,46,52,66,67,106] One study[37] used AUCs based on five serum samples. The number of samples was not reported in three studies.[31,34,43]

Single sample limited sampling strategies included predose (i.e., C_0, C_{min}, or C_{12}) in 59 studies,[7,8,11,12,14-20,22,24-28,30,32,33,36-42,44-50,52-62,64,66-76,106,120] 2 hour post dose concentration (C_2) in two studies,[54,57] peak (or maximal or C_{max}) in 11 studies,[11,17,26,36,43,51,52,54,66,75,76] C_{30min} in two studies,[33,67] C_{40min} in three studies,[21,54,66] and C_{60min} in two studies[33,54] Three sample limited sampling strategies included AUC based on C_0, $C_{0.5}$, C_2[43,63,64,77] AUC based on C_{20min}, C_1, C_3,[10] and AUC based on C_0, C_{75min}, C_4.[17,26] Four sample limited sampling strategies included AUC based on C_0, C_1, C_2, C_4[57] and AUC based on C_0, C_1, C_3, C_6.[13,59,65] The five sample limited sampling strategy included AUC based on C_0, C_{20min}, C_{40min}, C_{75min}, C_{120min}.[17-21,26] The seven sample limited sampling strategy included AUC based on C_0, C_1, C_2, C_3, C_4, C_6, C_9.[76] A final strategy was AUC_{0-9} (sampling times not provided).[49]

Rejection. Thirty studies, (32 reports) contained evidence showing that a method of MPA monitoring is associated with incidence of rejection (Tables 7 to 10).[7,8,10-12,17,19,26-33,38-49,54,57,59,63,64] Conversely, 29 studies, (30 reports) contained evidence against such associations (Tables 11 to 14).[11,13,15,17,19,24-26,28,34-37,42,45,49-62,65]

In the first published RCT that involved direct, head-to-head comparisons of monitoring versus no monitoring, Le Meur et al.[10] found that the incidence of treatment failure (composite of death, graft loss, acute rejection, and MMF discontinuation) was significantly lower in the concentration-controlled group (that used LSS of C_{20min},C_1, and C_3 developed by Bayesian methods, to target an AUC of 40 mg h/L) compared with the fixed dose group (29.2 percent vs. 47.7 percent, p=0.03). The percentage of acute rejection (12.3 percent vs. 30.7 percent, p=0.01) and biopsy-proven acute rejection (7.7 percent vs. 24.6 percent, p=0.01) were also lower in the concentration-controlled group. Cox proportional hazards regression analyses also found that the group factor (concentration-controlled vs. fixed dose) was the most powerful indicator of acute rejection (hazard rate ratio [HRR]=1.67, p=0.017); after other nonsignificant variables were deleted, the group factor was the only significant predictor of acute rejection (HRR=1.65; 95 percent CI=1.09, 2.54; p=0.02).[10]

An RCT[11,12] in which kidney transplant recipients were assigned to one of three pre-defined MPA AUC_{0-12} showed incidences of biopsy proven acute rejection to be 27.5 percent, 14.9 percent, and 11.5 percent respectively in each group (p=0.043). Although all three target values were exceeded after day 21, there was a significant association between the median natural logarithm of MPA AUC_{0-12} and biopsy proven acute rejection (p<0.001). Based on logistic regression analysis, MPA AUC_{0-12} values of 15 mg·h/L, 25 mg·h/L, and 40 mg·h/L are expected

to yield 50 percent, 75 percent, and 90 percent of maximal achievable efficacy (with a 4 percent change in efficacy for every 1 mg·h/L change in AUC at the midpoint of the logistic curve). Univariate logistic regression p-values between biopsy proven rejection vs. MPA $AUC_{0\text{-}12}$, MPA C_{max}, MPA C_0, and MMF dose were: < 0.0001, 0.0008, 0.0049, and 0.0918, respectively. The authors write that statistical significance is lost when only the first three predose concentrations are used in the logistic regression analysis. Consequently, they caution against basing dosage adjustments on a limited number of predose concentrations.[12]

Another study (two reports)[7,8] reported rejection outcomes for patients on fixed dose MMF (phase I) versus patients whose MMF dose was adjusted to meet target MPA predose concentrations of 2.5 to 4.5 mg/L (phase II). In the phase I group, the mean MPA predose concentrations were 3.6 mg/L with no episodes of rejection, 2.2 mg/L with one or two rejection episodes, and 1.5 mg/L with three rejection episodes (p-value not provided). In the phase II group, three patients (all of whom experienced only one rejection episode each) had MPA predose concentrations of 0.7 mg/L, 1.3 mg/L, or 0.9 mg/L. The authors also suggested that mean MPA plasma predose concentrations greater than 3.0 mg/L were not associated with rejection, although no details were provided in the reports.

In an RCT of kidney transplant recipients, Hazzan et al.[28] found that an MPA $AUC_{0\text{-}12}$ cut off of 50 mg·h/L was associated with risk for acute rejection in a multivariable Cox regression analysis (adjusted hazard ratio: 0.79; 95 percent CI: 0.64 to 0.98). The authors suggested that this cut off "needs to be confirmed by further investigations". In the same study, an MPA predose concentration cut off of 0.5 mg/L was not associated with risk for acute rejection in the multivariable model, but it was associated in a simple Cox model (unadjusted hazard ratio: 0.53; 95 percent CI: 0.30 to 0.94).

In nine case series, ROC curves were generated to determine whether a particular PK parameter could differentiate patients with acute rejection from patients without acute rejection. Weber et al.[26] found that C_0, C_{12}, $AUC_{0\text{-}12}$, and AUC (based on C_0, C_{75min}, C_4) were able to differentiate between pediatric kidney transplant recipients with and without acute rejection. An $AUC_{0\text{-}12}$ of 33.8 mg.h/L (measured using HPLC assay) had a diagnostic sensitivity of 80 percent and a diagnostic specificity of 57 percent; $AUC_{0\text{-}12}$ (measured using EMIT assay) was 36.1 mg.h/L. A C_{12} (HPLC) of 1.2 mg/L had a diagnostic sensitivity of 80 percent and a diagnostic specificity of 60 percent; C_{12} (EMIT) was 1.4 mg/L. In contrast, C_{max} and AUC (based on C_0, $C_{0.5}$, C_2) did not perform as well (p=0.24 and p=0.06 respectively) in differentiating between rejectors and non-rejectors.[26] Weber et al.,[17] in a second case series of pediatric kidney transplant recipients, found MPA C_{12}, $AUC_{0\text{-}12}$, AUC (based on C_0, C_{75min}, C_4), and AUC (based on C_0, $C_{0.5}$, C_2) were able to differentiate between patients with and without acute rejection. An $AUC_{0\text{-}12}$ (HPLC) of 33.8 mg·h/L had a diagnostic sensitivity of 75 percent and a diagnostic specificity of 64.3 percent. A C_{12} (HPLC) of 1.2 mg/L had a diagnostic sensitivity of 83.3 percent and a diagnostic specificity of 64.3 percent. Conversely, C_0 and C_{max} did not perform as well (p=0.07 and p=0.10 respectively) in differentiating between rejectors and non rejectors. In their third case series of pediatric kidney transplant recipients, Weber et al.[63] again found that AUC (based on C_0, $C_{0.5}$, C_2) was able to differentiate between patients with and without rejection. An AUC cut off of 36.8 mg·h/L had a prognostic sensitivity of 66.7 percent and a prognostic specificity of 61.9 percent.[63]

Results from the other six case series are as follows: Armstrong et al.[27] showed that an MPA $AUC_{0\text{-}12}$ cut off of 29.5 mg·h/L (HPLC) for acute rejection in pediatric kidney transplant recipients had a diagnostic sensitivity of 66.7 percent and a diagnostic specificity of 79.4

percent; MPA AUC_{0-12} cut off was 36.1 mg·h/L (EMIT). An MPA C_0 cut off of 1.0 mg/L (HPLC) for acute rejection had a diagnostic sensitivity of 77.8 percent and specificity of 64.5 percent; MPA C_0 (EMIT) was 1.3 mg/L.[27] The ROC curve analysis performed by Lu et al.[48] in kidney transplant recipients showed significant correlations between MPA C_0 and clinicial events (toxity and rejection), and revealed a diagnostic sensitivity (65.1 to 84.6 percent) and specificity (74.7 to 84.7 percent). Pawinski et al.[64] found that an AUC (based on C_0, $C_{0.5}$, C_2) cut off of 27.5 mg·h/L for acute rejection in kidney transplant recipients had a diagnostic sensitivity of 81.2 percent and a diagnostic specificity of 93.4 percent. The C_0 cut off for acute rejection of 1.1 mg/L had a diagnostic sensitivity of 63.4 percent and a diagnostic specificity of 85.3 percent. In a similar case series, Pawinski et al.[43] found that an AUC (based on C_0, $C_{0.5}$, C_2) cut off of 24.1 mg·h/L for acute rejection had a diagnostic sensitivity of 77.8 percent and diagnostic specificity of 91.7 percent. A C_0 cut off of 0.8 mg/L had a diagnostic sensitivity of 59.3 percent and diagnostic specificity of 83.3 percent. A C_{max} cut off of 5.1 mg/L had a diagnostic sensitivity of 66.7 percent and diagnostic specificity of 87.5 percent. Borrows et al.[14] found that a median MPA C_0 of 1.60 mg/L best differentiated between kidney transplant recipients with and without acute rejection in the first 30 days post transplant. However, no association was observed between MPA concentration and five specific acute rejection episodes that occurred after 30 days. Kiberd et al.[57] found that the best cut off point for predicting rejection in kidney transplant recipients was an AUC (based on C_0, C_1, C_2, C_4) of 22 mg.h/L (sensitivity 82 percent, specificity 64 percent, negative predictive value 89 percent, positive predictive value 30 percent).

Graft function or other efficacy parameter. Two studies[18,106] looked at methods of MPA monitoring and the incidence of graft function (Tables 15 and 16). The first study[18] was a case series involving 46 stable kidney transplant recipients. Graft function was defined by creatinine clearance (severe graft dysfunction: creatinine clearance less than 20 mL/min). Patients with an MPA AUC_{0-12} cut off greater than 40 µg/mL·h had better graft function than patients with an MPA AUC_{0-12} of 40 µg/mL·h or less. Mean creatinine clearance values were 85.7 mL/min in the 'greater than' group and 64.5 mL/min in the 'less than' group ($p<0.01$). The authors claimed to have similar findings for an MPA predose concentration (AUC_{0-2}) cut off of 1.5 µg/mL, but no data were reported. MPA AUC_{0-12} was significantly and positively correlated with creatinine clearance ($r=0.52$, $p< 0.01$), as was predose concentration (MPA AUC_{0-2}) ($r=0.50$, $p< 0.01$).

A case control study[106] of 27 stable kidney transplant patients looked at the correlation of MPA AUC_{0-12}, C_{min}, and C_{max} with IMPDH (Inosine 5'-Monophosphate Dehydrogenase) activity, a direct pharmacodynamic parameter of MPA. Although the authors reported that "for the majority of the patients an inverse relationship between MPA concentrations and IMPDH activity was observed", patients with comparable MPA AUC_{0-12}, C_{min}, and C_{max} values exhibited different degrees of IMPDH inhibition, which suggests wide interindividual pharmacodynamic activity. Furthermore, in MPA-treated patients, baseline IMPDH differences may lead to differences in outcome.

Adverse events. Four studies showed that full AUC (AUC_{0-12}) is associated with adverse events. One of these studies was a non randomized controlled trial[31] and the three others were case series.[33,36,46] There were 18 positive studies involving predose concentrations (predose, C_0, C_{min}, or C_{12}): one was an RCT,[68] three were prospective cohort studies,[39-41] and 14 were case series.[14,16,33,36,45,48,56,61,69-74] Five studies found other limited sampling strategies to be related to adverse events: one was an RCT evaluating C_0, C_1, C_3, and C_6[65] and four were case series (one of C_{40min},[66] one of C_0, C_1, C_3, and C_6,[59] one of both C_{30min} and C_{60min},[59] and one of C_{30min}[67]). No studies found C_2 to be a significant predictor of adverse events (Tables 17-20).

Eleven studies showed that full AUC (AUC_{0-12}) is not associated with adverse events. Two of these studies (three reports) were randomized controlled trials,[11,12,29] two were prospective cohort studies,[35,52] and seven were case series.[17,26,32,36,37,66,67] There were 24 negative studies of predose (C_0, C_{min}, or C_{12}): three (four reports) were RCTs,[11,12,25,75] one was a non randomized controlled trial,[49] two were prospective cohort studies,[20,52] one was a case control study,[54] two were retrospective cohort studies,[22,42] and 15 were case series (Tables 21 to 24).[14,15,17,18,26,36,37,47,57,62,64,66,67,72,76]

Two studies (a case control[54] and a case series[57]) found C_2 not to be a significant predictor of adverse events. Of 16 studies finding other limited sampling strategies to be unrelated to adverse events, one was a RCT directly comparing fixed dose versus targeted AUC values based on a limited sampling strategy (LSS) of C_{20min}, C_1, C_3[10], two were RCTs evaluating C_{max},[11,75] one was a non randomized controlled trial of AUC_{0-9}[49], 3 were prospective cohort studies (one of C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min},[20] one of C_0, C_1, C_3, and C_6[13], and one of C_{max}[52]), one was a case control study of 3 different LSSs (i.e., C_{40min}, C_{60min}, and C_{max}),[54] and 8 were case series (one evaluating both C_0, C_1, C_2, C_4, C_6, and C_9 as well as C_{max},[76] one of C_0, $C_{0.5}$, and C_2,[64] two of C_{max},[36,66] one of C_0, C_1, C_2, and C_4,[57] two evaluating 3 different LSSs of C_{max}, AUC_{0-4} or C_0, C_{75min}, and C_4, and AUC_{0-2} or C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min},[17,26] and another evaluating C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min}[21]).

A secondary objective of the Le Meur et al. RCT[10] was to compare the incidence of adverse events in the concentration-controlled versus the fixed dose groups. Overall, 97 percent and 90 percent of patients in the concentration-controlled and fixed dose groups, respectively, reported one (or more) adverse events. There was no significant difference ($p>0.05$) in incidence of total adverse events and specific gastrointestinal events, anemia, leucopenia, or infections between the two groups, except for herpes infections which occurred more frequently in the concentration-controlled group (8 vs. 1 event, $p<0.05$).[10]

The van Gelder et al.[12] and Hale et al.[11] RCT in kidney transplant patients compared adverse events for subjects with planned dose adjustments based on different target MPA plasma concentrations.[11,12] They found that premature study withdrawal due to adverse events was not associated with the median natural logarithm of MPA AUC_{0-12} ($p=0.434$) nor the median natural logarithm of C_0 ($p=0.512$). Associations between each specified adverse effect (i.e., diarrhea, nausea, leucopenia, CMV, urinary tract infection, and abdominal pain) and MPA AUC_{0-12}, MPA C_{max}, and MPA C_0 were all not statistically significant ($p>0.05$).[11] One explanation for the lack of statistically significant associations is that the data anlysis in the trial was undertaken before the ascertainment of total MPA concentrations over time post transplant. Median AUC was used instead, and patients with higher median AUCs tended to remain in the study longer than patients with adverse events.[6]

A case series conducted by Hubner et al.[56] in kidney transplant recipients reported adverse events for subjects with planned dose adjustments based on MPA predose concentrations. The data showed that MPA predose concentrations for patients with adverse events were higher relative to patients without adverse events (2.13 versus 1.53 mg/L; $p< 0.001$). Shaw et al.[20] evaluated two groups of kidney transplant recipients (i.e., MPA AUC-controlled versus MPA C_0-controlled dose adjustment) and stated that the occurrence of diarrhea was not associated with high concentrations of MPA AUC, predose, or MPAG predose values. However, they did not provide quantiative data for their claim.[20]

In three case series,[14,33,48] the authors generated ROC curves to determine whether a particular PK parameter could differentiate between patients with and without adverse events.

Mourad et al.[33] found that an MPA C_0 cut off of 3 mg/L for toxicity in kidney transplant recipients had a diagnostic sensitivity of 38.7 percent and a diagnostic specificity of 91.5 percent. An MPA C_{60min} cut off of 8.09 mg/L for toxicity had a diagnostic sensitivity of 77.8 percent and a diagnostic specificity of 67.4 percent. Lastly, an MPA AUC_{0-12} cut off of 37.6 mg·h/L for toxicity had a diagnostic sensitivity of 83.3 percent and a diagnostic specificity of 59.6 percent. The ROC curves were not statistically significantly different between these parameters.[33] Borrows et al.[14] found the median C_0s that best discrimated between patients with and without the following adverse events: leucopenia (2.60 mg/L), anemia (2.75 mg/L), diarrhea (2.40 mg/L), and viral infection (3.20 mg/L). The Lu et al.[48] ROC analysis showed significant correlations between MPA C_0 and clinicial effects (rejection and toxicity) in kidney transplant recipients,with a dignostic sensitivity of 65.1 to 84.6 percent and specificity of 74.7 to 84.7 percent.

Question 4. Does the Evidence for Monitoring MPA Differ by any of the Following?

Forty eight studies were included to address the six components of the key question. Study characteristics are shown in Evidence Table 1, Appendix C*.

4a: Age

Six studies[17,18,23,69,112,122] addressed the effect of age on MPA PK parameters in kidney transplant patients. Three of these studies included adult patients only,[18,69,122] two included pediatric patients only,[17,23] and one compared pediatric with adult kidney transplant patients.[112] One other study involved pediatric heart transplant patients.[55] The findings of these studies (Table 25) are summarized below.

One of the adult only studies (n=117) of kidney transplant patients did not find an association between age and MPA predose concentrations.[69] The other adult study (n=46) found that patients in the MPA AUC_{0-12} >40 μg/mL·h group were slightly but significantly younger than patients in the <40 μg/mL·h group.[18]

Wang et al. compared the pharmacokinetic characteristics of MPA among elderly (defined as over 60 years of age) Chinese renal transplant recipients (n=24) to younger adults (n=24).[122] This study found that the MPA AUC was significantly lower in the elderly compared to the younger adult group receiving the same dose of MMF, although the differences in predose, peak concentrations, or peak times were not significant.[122]

Turning to the pediatric only studies, the Bunchman et al.[23] multicenter, open label, single arm study of MMF oral suspension (n=100) showed no clinically significant differences in MPA and MPAG PK parameters among different age groups. No associations were observed between low MPA and MPAG plasma concentrations and the incidence of acute rejection. Similarly, no associations were found between adverse events and PK parameters. Conversely, an open label, longitudinal evaluation of the PK-pharmacodynamic relationship for total and free MPA in pediatric kidney transplantation (n=54) by Weber et al.,[17] showed that in the first week post transplant, but not at later, PK sampling periods, low MPA AUC_{0-12} values were associated with young age. The same study showed that both MPA AUC_{0-12} and predose MPA concentrations were significantly associated with the risk of acute rejection in this patient population. By ROC

* Appendixes and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/clinic/tp/mpaorgtp.htm

analysis, an AUC_{0-12} of 33.8 mg·h/L in the initial phase post transplant had a diagnostic sensitivity of 75 percent and a diagnostic specificity of 64 percent for discrimination of patients with acute rejections. The respective discrimination threshold for the MPA predose concentrations was 1.2 mg/L, with a sensitivity of 83 percent and a specificity of 64 percent.

In the Weber et al.[112] pediatric (n=18) versus adult (n=10) kidney transplant study, which was an open label, prospective study to evaluate MPA PK parameters, children displayed concentration-time profiles of total and free MPA after oral administration of 600 mg/m^2 body surface area twice daily that, in general, were comparable to the profiles of adults receiving 1,000 mg MMF twice daily. This was in the first three weeks post transplant. Mean MPA AUC_{0-12} in pediatric patients one week post transplant was 40 percent higher than in adults, but comparable at three weeks. The AUC_{0-12} values of free MPA at one and three weeks did not differ between children and adults. The authors found higher AUC_{0-12} values for the MPA metabolite MPAG in adult patients compared with children, but this was most likely due to the higher incidence of primary transplant dysfunction in the adults.[112]

The Dipchand et al.[55] retrospective study involving pediatric heart transplant recipients (n=44) found that increased MPA predose concentrations were significantly associated with older children, thereby implying that higher MMF doses may be required to achieve appropriate MPA concentrations in very young patients.

4b: Gender

The literature search failed to yield studies of direct relevance to this question. Ideally, studies to answer this question would examine the relationship between MPA PK parameters and patient outcomes (e.g. rejection, adverse events) for men versus women. However, three studies[29,52,69] in kidney transplant patients did examine associations between gender and MPA PK parameters (Table 26). Of these studies, two[29,69] reported a difference in MPA PK parameters between men and women, while the third[52] reported no difference. None of the studies examined how the associations might affect patient outcomes.

The Lu et al.[29] open label, randomized evaluation of MPA PK parameters in Chinese primary kidney transplant patients (n=29) showed a statistically significant difference in MPA AUC_{0-12} according to gender. MPA AUC for females was higher than that of males by 34.3 percent even though females were receiving the same doses of MMF (p=0.0006). In this study, MPA AUC_{0-12} was lower in the patients who experienced an acute rejection compared to patients who did not (40.93 $\pm$ 14.28 μg·h/ml versus 53.88 $\pm$ 12.70 μg·h/ml; p=0.038). However, MPA AUC_{0-12} values were not stratified by gender. Similarly, in the Borrows et al.[69] prospective study of kidney transplant recipients (n=117), multivariable analysis showed that female gender was associated with higher predose concentrations compared to males (effect size: 1.22; 95 percent CI: 1.12 to 1.31; p=0.002). In contrast, a prospective study, by Kuypers et al.,[52] of 100 de novo, deceased donor, renal transplant patients showed that MPA PK parameters were not influenced by recipient gender. The same study found no significant relationship between acute rejection and MPA AUC_{0-12}, C_0, or C_{max}.

4c: Ethnicity

Two studies[20,69] retrieved in the literature search contained data linking ethnicity and MPA PK parameters (Table 27). Both studies involved kidney transplant patients and suggested there is no association between ethnicity and MPA PK parameters.

The Shaw et al. study[20] found no significant differences in MPA AUC values over the three month study period in African Americans (n=13) compared to Caucasians (n=20). The MPA predose concentrations were also not statistically significantly different between groups, although the values were generally higher in African Americans. The incidence of acute rejection at three months was 30.8 percent in the African Americans and 15 percent in the Caucasians (p=0.288). The authors suggest that the difference in acute rejection rates may have been due to differences in immune response. Regarding adverse events, the occurrence of diarrhea was not associated with high concentrations of either total or free MPA AUC, predose, or MPAG predose values. The Borrows et al. study[69] (n=117) showed no association between ethnicity (White, Indo-Asian, Afro-Caribbean, other) and MPA predose concentrations.

4d: Concomitant use of Calcineurin Inhibitors (e.g., Tacrolimus, Cyclosporine)

Studies of direct relevance to this question compared one calcineurin inhibitor (CNI) to another in terms of patient outcomes (e.g., acute rejection or adverse events) related to MPA monitoring. Other studies addressed the effects of CNIs on MPA PK parameters. In our search, we found 12 such studies involving renal transplant patients,[13,29,33,36,38,49,63,64,69,76,77,108] three involving cardiac transplant patients,[45,58,70] and two involving liver transplant patients.[40,107] An additional study compared liver and small bowel transplant recipients to renal transplant recipients (Table 28).[24]

Most studies found that the type of concomitant CNI used for maintenance immunosuppression influenced MPA PK parameters. Seven studies of renal transplant recipients (n=29 to 290)[13,29,33,38,64,76,77] and two studies of cardiac transplant recipients (n=20 to 26)[45,58] showed that patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations compared to patients receiving concomitant cyclosporine. For example, in Atcheson et al.'s prospective study[13] of 42 de novo renal transplant patients, patients in the cyclosporine treated group had a mean total MPA predose concentration (for the same dose of MMF) that was approximately half of what patients had in the tacrolimus treated group. Most of these studies also found that not only the predose, but the MPA AUC as well, was significantly higher with co-administration of tacrolimus compared to cyclosporine.[29,33,64,76,77] In the recent Heller et al. study[77] performed as a sub-study of a phase IV open, prospective, randomized controlled trial comparing fixed dose versus concentration-controlled MMF regimens for renal transplant recipients, though MPA AUC was higher in patients on concomitant tacrolimus compared with cyclosporine, the plasma AcMPAG and MPAG concentrations were substantially lower in the former group. These data support the assumption that cyclosporine inhibits the biliary excretion of MPAG and AcMPAG, therefore potentially reducing the risk of intestinal injury through enterohepatic recycling of MPA and its metabolites. In this study significantly more patients on tacrolimus suffered from diarrhea compared to cyclosporine (31.1 percent versus 12.7 percent, respectively).

One study, by Naito et al.,[108] involving 25 Japanese renal transplant recipients showed no significant difference in MPA predose concentrations between tacrolimus versus cyclosporine treated groups. There was also no difference in CNI treated patients compared with patients not receiving concomitant CNIs. The Tredger et al. study[40] evaluating 95 adult liver transplant patients found median MPA concentrations were lower with tacrolimus than with either cyclosporine or no CNI comedication.[40] Ringe et al.[107] found that a two hour dosing interval between MMF and Tacrolimus reduced MPA related diarrhea, resulting in higher Tacrolimus levels.[107]

4e: Concomitant use of Other Medications

Five studies with relevance to this question were retrieved in the literature search (Table 29).[22,50,65,69,78] The Mudge et al.[65] open label, RCT in renal transplant recipients (n=40) found no significant effect of oral iron supplements on MMF absorption as measured by MPA AUC measurements. Patients who experienced toxicity showed significantly higher MPA AUC measurements than those who tolerated MMF well. However, there were no significant differences in the occurrence of MMF toxicity between the three groups of no iron versus iron with morning MMF dose versus iron spaced four hours apart from morning MMF dose. There were also no differences between the three groups in the observed frequencies of anemia, leucopenia, thrombocytopenia, infection or gastrointestinal intolerance. Rejection rates were similar between the study groups.

A randomized, open label, crossover study, by Wolfe et al.,[78] involving 12 male kidney transplant recipients evaluated the PK parameters of MPA in patients given 1,500 mg oral MMF alone, MMF and 5 mg/kg intravenous ganciclovir, and ganciclovir alone in separate phases with at least a one week washout period in between. The single dose PK parameters of MPA and its glucuronide metabolite, MPAG, were unchanged by the addition of ganciclovir. Neither the renal elimination nor the metabolism of MPA to MPAG was altered with the addition of ganciclovir, as indicated by the percentage of dose excreted as MPAG and the MPAG:MPA AUC ratio.

The Borrows et al. study[69] involving 117 renal transplant patients found that treatment with oral augmentin, ciprofloxacin, or metronidazole was associated with a reduction in MPA predose concentrations, but no effect was seen with the use of intravenous antibiotics (vancomycin, tazocin, and carbopenems). The authors explain the lower MPA predose concentration in patients treated with oral antibiotics as being due to a reduction of enterohepatic circulation. An antibiotic induced reduction in enteric organisms possessing glucuronidase leads to decreased recycling of MPAG back to MPA within the bowel and to a consequent reduction in the secondary peak of MPA absorption. The same study found no association between MPA predose concentrations and the use of oral prednisolone, ferrous sulfate, calcium carbonate, or ganciclovir.

Merkel et al.'s[22] retrospective study of 35 kidney transplant recipients showed no effect of concomitant steroids or furosemide on MPA or MPAG predose concentrations. The same study showed a positive correlation between xipamide (a thiazide diuretic) and MPA predose and a negative correlation between diltiazem and MPA predose.

Kreis et al.'s[50] randomized trial of kidney transplant patients (n=78) receiving sirolimus or cyclosporine showed that the average daily doses of MMF were significantly lower in the

sirolimus group, while MPA predose concentrations were significantly higher in the sirolimus group.

4f: Comorbidity

Studies addressing the effect of renal function on MPA PK parameters provided mixed findings (Table 30). In one study of 46 kidney transplant patients, plasma MPA predose concentrations and MPA AUC_{0-12} were positively and significantly correlated with patients' creatinine clearance values.[18] A Japanese study involving 25 kidney transplant patients found that MPA and MPAG predose concentrations were influenced by renal function in cyclosporine treated recipients, but not in patients treated with tacrolimus.[108]

In a study comparing eight kidney transplant patients with renal insufficiency (defined as creatinine clearance < 20 ml/min) and 15 renal transplant patients with preserved renal function, Kaplan et al.[21] found that the average free fraction of MPA and the free MPA AUC was approximately double in patients with chronic renal insufficiency compared to patients with normal renal function. MPAG average concentrations in patients with renal insufficiency were significantly higher than patients with preserved renal function. Half of the patients with chronic renal insufficiency developed leucopenia within one month of the kinetic study. This adverse effect occurred in patients with the highest free MPA AUC. None of the patients with preserved renal function developed this complication.[21] In another study, Shaw et al.[20] found that impaired renal function lowered the MPA AUC in both African Americans and Caucasians in the early post transplant period. This was attributed to an increased free fraction of MPA in the patients with graft dysfunction as a result of reduced binding of MPA to serum albumin. An open label prospective study evaluating the MPA PK parameters in pediatric kidney transplant patients (n=18) compared with adults (n=10) reported a tight inverse correlation between plasma MPAG AUC_{0-12} values and GFR both in children ($r=-0.70$, $p<0.001$) and adults ($r=-0.83$, $p<0.001$).[112]

In another study (n=31), Johnson et al.[123] stratified subjects based on their iohexol clearance and found that MPA clearance was not associated with changes in GFR. C_{max} tended to increase as GFR decreased. MPAG clearance correlated well with GFR ($r^2=0.90$). Clearance of MPA and MPAG were unaffected by hemodialysis, with losses during hemodialysis representing less than 10 percent of the dose administered. Morgera et al.[116] studied the impact of peritoneal dialysis on MPA PK parameters in five patients following renal transplantation. MPA and MPAG AUC decreased during peritoneal dialysis.

In a randomized, placebo controlled trial (n=57 renal transplant patients), the concentrations for MPA were not affected by graft function or dialysis; however, there was an increase of MPAG with decreasing graft function.[25] In a study of eight kidney transplant patients, renal dysfunction was associated with altered PK parameters of MPA, particularly increased AUC_{0-12} of MPAG, MPA free fraction, and AUC_{0-12} of free MPA. The perturbed PK parameters normalized with improving renal function.[113] Another prospective study evaluated the impact of peritoneal dialysis on the PK parameters of MPA in five kidney transplant recipients. They found a significant inverse correlation between GFR and MPA-AUC and between GFR and MPAG-AUC.[115]

The effect of liver function on MPA PK parameters is not entirely clear. In the Zakliczynsk et al.[70] study of 76 cardiac transplant patients, a significant positive correlation was observed between MPA concentrations and cyclosporine in patients with impaired liver function. However, no correlation was noted between MPA predose and cyclosporine in patients without

liver dysfunction. Brunet et al.[66] found no significant correlation when the effect of liver function tests on MPA concentration and AUC was examined in 15 primary cadaveric liver transplant recipients.

In another study, by Naesens et al.,[79] involving 95 kidney transplant recipients, investigators evaluated the association between single nucleotide polymorphisms (SNP) in the MRP2 gene and MPA PK parameters. In patients not carrying the MRP2 C-24T SNP gene, the investigators found a marked difference in MPA exposure between patients with and without liver dysfunction. Patients with mild liver disease had significantly lower MPA dose corrected predose concentrations, a lower dose corrected MPA AUC_{0-12}, and higher calculated MPA clearance.

Question 4. Summary

Based on the current evidence available, some of the six components of this question appear to influence MPA PK parameters. However, none of the included studies investigated whether PK parameter levels, stratified by each component, were associated with outcomes such as rejection or adverse events. Regarding age, the evidence was equivocal. In pediatric populations, younger children were found to require a higher MMF dose to achieve a specified MPA concentration. Regarding gender, the evidence appears to indicate that PK parameters are higher for females versus males. Race and ethnicity do not appear to influence MPA PK parameters. Calcineurin inhibitors are co-administered frequently with MMF and the bulk of the evidence found that exposure to MPA is higher in patients receiving tacrolimus compared to cyclosporine, with lower doses of MMF required in combination with tacrolimus to achieve adequate MPA exposure. Total MPA PK parameters were generally higher in persons with renal insufficiency, although one study found lowered MPA AUC in the early post transplant period.

Question 5. What is the Short- and Long-Term Cost-Effectiveness of Avoiding Acute Rejection due to MPA Monitoring?

Findings from the abstracted studies. None of the abstracted studies contained any data on the cost-effectiveness associated with MPA monitoring. There is no evidence in the literature on the cost-effectiveness of MPA monitoring.

Quality Assessment of Abstracted Studies

Twelve of the 89 abstracted studies were RCTs[10-12,25,28,29,34,50,51,65,68,78] and the remainder were observational studies (primarily case series). The quality of the RCTs was fair to good. Eleven studies contained baseline comparisons of treatment groups (three had minor differences on one or two variables), 11 used ITT analyses, eight clearly reported the methods used to measure MPA, and 10 had clear definitions of outcomes related to measuring MPA. Conversely, reporting of some essential features of trial design was lacking. The method of randomization was described in five studies and the means of treatment allocation was described in two studies. The authors of three studies reported that subjects and persons assigned to measure MPA were blinded; four studies contained reports of blinding amongst outcome assessors. One of the RCTs[10] contained reports of differential losses to followup. Although it appears from the

published reports that there were no losses to followup in the other reports, the authors did not specifically state whether any such losses occurred.

Compared to the RCTs, the 77 observational studies suffered from numerous reporting problems. Virtually all of the studies lacked reports of blinding among subjects (n=73), persons measuring MPA (n=74), and outcomes assessors (n=75). Differential losses to followup were not reported in 61 studies. The authors of only 29 studies made an attempt to control for confounding. Some aspects of reporting were good, though, as the authors of most of the observational studies described the methods used to measure MPA (n=68) and clearly defined their outcomes (n=69).

The most troublesome aspects of study quality were the failure to report blinding in a majority of the studies and the failure to control for confounding in most of the observational studies. For blinding, it is often debatable whether the issue reflects poor study quality or poor reporting. For confounding, the very nature of observational studies suggests that the influence of 'third party' variables should be considered in the design or analysis stage. To do otherwise is a serious omission.

Table 1. Studies showing that rejection is related to MMF dosage

Study	Population	Treatment	Major Findings/ Comments
Satoh[35] 2005 Study design: Prospective Cohort Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age: Mean AZA: 37.9 +/- 11.5y MMF: 44.3 +/- 11.6y	Dose: 1.0 – 2.0 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone	MMF dose per bodyweight was lower in patients with AR than those without AR (25.1 vs. 35.6 mg/kg, p=0.026) but there was no significant difference in MPA AUC_{0-12} in patients with AR compared to those without AR (32.2 vs. 59.5 μg·h/L, p=0.081)
Satoh[30] 2006 Study design: Case series Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 41.2 +/- 2.1y Range 21 – 66y	Dose: 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Corticosteroids	Single dose/bodyweight in patients with and without AR were 12.46 and 16.99 mg/kg, respectively (p=0.024)
Takahashi[31] 1995 Study design: Non randomized controlled trial Length of followup: 12 weeks	Organ: Kidney Age: Inclusion requirement ≥16y 1000 mg/d: Mean 37.7 ± 6.3 y 2000 mg/d: Mean 38.5 ± 12.2 y 3000 mg/d: Mean 41.0 ± 10.3 y	Dose: 1000, 2000, or 3000 mg/day Concomitant medications: Cyclosporine Steroids (no description)	The following percentages of patients did not experience rejection episodes in the 1000 mg, 2000 mg, and 3000 mg MMF dose groups: 25.0%, 55.6%, and 80.0%, respectively (p values not given)

Abbreviations: AR=Acute rejection, AUC=Area-under-the-concentration-time curve, AZA=Azathioprine, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not reported, y=Years

Table 2. Studies showing that rejection is not related to MMF dosage

Study	Population	Treatment	Major Findings/ Comments
Barbari[53] 2005 Study design: Case control Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 39y Range 20 – 67y	Dose: 1 g BID range 1 - 2.5 g/day Concomitant medications: Cyclosporine Prednisone	There was a poor association between clinical events (primarily rejection, but also lymphocyte counts [an indicator of immune responsiveness]) and MMF dosage or MPA predose concentrations (r=0.0803).
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18 y Range: L: 47.8 +/- 11.5 y, I: 46.9 +/- 13.8y, H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adj I: 0.95 g BID then adjusted H: 1.7 g BID then adjusted Concomitant medications: Cyclosporine Corticosteroids	Univariate logistic regression p values between biopsy-proven rejection vs. MPA AUC_{0-12}, MPA C_{max}, MPA C0, and MMF dose were: < 0.0001, 0.0008, 0.0049, and 0.0918, respectively (i.e., not significant for MMF dose). In bivariate logistic regression analysis, MPA AUC remains statistically significant, but MPA C_{max}, MPA C0, and MMF dose are all not significant.
Hazzan[28] 2005 Study design: RCT Length of followup: 1 year	Organ transplanted: Kidney (Renal) Age: Mean CsA 42.5 +/- 12.1y MMF 45.1 +/- 11.2y	Dose: CsA group MMF dose = 1.93 +/- 0.2 g/day then withdrawn to 0, MMF group MMF dose = 1.99 +/- 0.1 g/day Concomitant medications: Cyclosporine	No significant difference was observed in MMF dose between patients with AR and those without (2.0 vs. 1.9 g/day).
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study subjects as Kuypers[52] MMF dose was not significantly different in patients with acute rejection compared with those without (17.6 $mg \cdot kg^{-1} \cdot day^{-1}$ vs. 20.9 $mg \cdot kg \cdot day$, p=0.16).

Abbreviations: ADJ=Adjusted, AR=Acute rejection, AUC=Area-under-the-concentration-time curve, BID=Twice Daily, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, CsA=Cyclosporin A, H=High, I=Intermediate, L=Low, MMF= Mycophenolate Mofetil , MPA=Mycophenolic Acid, NR=Not Reported, RCT=Randomized Controlled Trial, y=Years

Table 2. Studies showing that rejection is not related to MMF dosage (continued)

Study	Population	Treatment	Major Findings/ Comments
Kuypers[52] 2003 Study design: Prospective Cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 1 g/day or 2 g/day Concomitant medications: Cyclosporine Tacrolimus Methylpredisolone 31 patients received daclizumab	Same study subjects as Kuypers[36] The percentage of patients with biopsy-proven acute rejection did not differ between the 1- and 2-g MMF groups. One-year patient and graft survival also was not significantly different between the 1- and 2-g MMF groups.
Mourad[33] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 32-68y Median 49y	Dose: 500 mg BID + adjustment for side effects Concomitant medications: Tacrolimus Corticosteroids	MPA measurements at the time of acute rejection for 3 patients (5.8%) at a fixed dose of 500 mg twice daily were: MPA C0 of 1.86, 1.76, and 3.83 mg/L; MPA AUC_{0-12} of 37.7, 24.9, and 104.9 mg.h/L.
Yamani[42] 2000 Study design: Retrospective Cohort Length of followup: 179 +/- 52 days	Organ transplanted: Heart (Cardiac) Age: Mean 36 +/- 14y	Dose: 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	There was no significant difference in mean MMF dose or mean MMF predose concentrations between samples with and without rejection at any time post transplant.

Table 3. Studies showing that adverse events are related to MMF dosage

Study	Population	Treatment	Major Findings/ Comments
Bilbao[62] 2006 Study design: Case series Length of followup: mean 39 ± 20 months; range 3 to 72 months	Organ transplanted: Liver Age: Mean 59 ± 6y	Dose: Initial dose of 500 mg/12h; reaching dose of 1 g each 12h for 2 weeks. Concomitant medications: Cyclosporine (Neoral) Tacrolimus	Dose adjustments were based on tolerability and adverse events and not on predose concentrations although they "tried to avoid concentrations over 4 µg/mL".
Borrows[14] 2006 Study design: Case series Length of followup: minimum of 12 months; median 25 months; range 13-38 months	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 9y Range 37 – 55y	Dose: 750mg – 2g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone Corticosteroids Ganciclovir (for 3 months) Co-Trimoxazole (for 6 months) Isoniazid and Puridoxine (used in indo-asians and those with previous TB) Basiliximab or Daclizumab (79 patients)	In multivariate analysis, total daily MMF dose was significantly associated with anemia and MMF-associated diarrhea (p=0.002 and 0.003, respectively), but not with leucopenia, viral infection or acute rejection.
Borrows[69] 2005 Study design: Case series Length of followup: 30 months; median 19 months; range 6 – 30 months	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 9y Range 37-55y	Dose: 250-1500 mg/day corrected for body weight Concomitant medications: Tacrolimus Methylprednisolone Prednisone	A higher MMF dose had been given to patients with MMF-related diarrhea (1750 mg vs. 1371 mg, p=0.007).

Abbreviations: BID=Twice Daily, CsA=Cyclosporin A, GI=Gastrointestinal, H=High, I=Intermediate, L=Low, MMF=Mycophenolate Mofetil, RCT=Randomized Controlled Trial, y=Years

Table 3. Studies showing that adverse events are related to MMF dosage (continued)

Study	Population	Treatment	Major Findings/ Comments
Deierhoi[75] 1993 Study design: RCT Length of followup: phase I trial: mean 26 months; range 22 - 28 months; rescue: mean 20 months; range 16 - 24 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement phase I: older than 18y, Rescue: older than 16y	Dose: Phase I: 1500 - 3000 mg/day Rescue: 2000 mg/day and 3000-3500 mg/day if no response in first week Concomitant medications: Phase I: Minnesota antilymphocyte globulin(MALG) Methylprednisolone Cyclosporine Corticosteroids Rescue: Predisone Cyclosporine Minnesota antilymphocyte globulin(MALG) Azathioprine	Three patients (28%) required a dose reduction due to side effects (diarrhea, nausea, elevated liver enzymes) and responded to this dose reduction.
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18y Range L: 47.8 +/- 11.5; I: 46.9 +/- 13.8; H: 50.6 +/- 10.5	Dose: L: 0.45 g BID then adj : 0.95 g BID then adj H: 1.7 g BID then adj Concomitant medications: Cyclosporine Corticosteroids	The risk of diarrhea and the risk of premature study withdrawal due to adverse events were both significantly related to mean MMFdose.
Kuypers[15] 2003 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 49.4 +/- 13.1y	Dose: 1 g BID Concomitant medications: Methylprednisolone Tacrolimus Daclizumab	MMF doses were reduced by blinded investigators when patients experienced adverse events (leucopenia, GI intolerance, infections).

Table 3. Studies showing that adverse events are related to MMF dosage (continued)

Study	Population	Treatment	Major Findings/ Comments
Maes[16] 2003 Study design: Case series Length of followup: 2 years	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 15y Range 18 – 70y	Dose: 1.6 +/- 0.5 g/day, range 1 – 3 g/day Concomitant medications: Cyclosporine Tacrolimus Methylprednisolone	MMF dose reduction was the only effective therapy for a Crohn's disease-like enterocolitis. Thus, MMF (and/or MPA) may be a cause.
Merkel[22] 2005 Study design: Retrospective Cohort Length of followup: 16 months, mean 5.7 months	Organ transplanted: Kidney (Renal) Age: Mean 44 +/- 13.6y Range 13 – 63y	Dose: 0.5 - 1.0 g BID Concomitant medications: Cyclosporine Prednisone Corticosteroids	More adverse events occurred in patients treated with MMF 2 g/day vs. 1 g/day (p value not given).
Mourad[33] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 32-68y Median 49y	Dose: 500 mg BID + adjustment for side effects Concomitant medications: Tacrolimus Corticosteroids	MMF dose per body surface area (mg/m^2) twice daily was significantly higher in 31 patients (samples) who experienced adverse events compared with 47 patients (samples) who did not (294.77 vs. 278.02 mg/m^2, p=0.02).
van Besouw[72] 1999 Study design: Case series Length of followup: 8 months	Organ transplanted: Kidney (Renal) Age: Not reported	Dose: 2 g/d – 1 g/day Concomitant medications: Prednisone	Although MMF dose reduction from 2 g/day to 1.5 g/day did not increase hemoglobin concentration (p=0.12), after a further dose reduction to 1 g/day, the hemoglobin concentration in 20 out of 26 patients had reached pre-conversion (from CsA to MMF) concentrations (p=0.75). The authors summarized that "Not only the MMF dose but also the mycophenolic acid (MPA) predose concentration correlated with the Hb concentration".
van Gelder[12] 1999 Study design: RCT Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range L: 47.8 +/- 11.5y; I: 46.9 +/- 13.8y; H: 50.6 +/- 10.5y	Dose: L: 16.1 ug hr/ml I: 32.2 ug hr/ml H: 60.6 ug hr/ml Concomitant medications: Cyclosporine Prednisone Corticosteroids	Posthoc analysis showed that only the premature withdrawal due to GI (and not other) adverse events was significantly related to MMF dose. This suggests that high local, non-systemic, drug concentrations, may be responsible for the GI adverse events.

Table 4. Studies showing that adverse events are not related to MMF dosage

Study	Population	Treatment	Major Findings/ Comments
Barbari[53] 2005 Study design: Case control Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 39y Range 20 – 67y	Dose: 1 g BID range 1 - 2.5 g/day Concomitant medications: Cyclosporine Prednisone	There was a poor association between clinical events (primarily rejection, but also lymphocyte counts [an indicator of immune responsiveness]) and dosage or predose MPA concentrations
Borrows[14] 2006 Study design: Case series Length of followup: 38 months median 25 months range 13-38 months	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 9y Range 37 – 55y	Dose: 750 mg – 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone Corticosteroids Ganciclovir (for 3 months) Co-Trimoxazole (for 6 months_ Isoniazid and Puridoxine (used in indo-asians and those with previous TB) Basiliximab or Daclizumab (79 patients)	In multivariate analysis, total daily MMF dose was not significantly associated with leucopenia, viral infection or acute rejection, but was significantly associated with anemia and MMF-associated diarrhea (p=0.002 and 0.003, respectively)
Heller[77] 2007 Study design: Prospective cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 53.4y	Dose: Fixed dose group: 1 g BID, Concentration-controlled group: target concentration of 30-60 mg*h/L Concomitant medications: Cyclosporine Tacrolimus	Mean MMF daily doses were not significantly different between patients with diarrhea versus those without.

Abbreviations: AUC=Area-under-the-concentration-time curve, AZA=Azathioprine, BID=Twice Daily, C_{max}=Maximum Serum or Plasma Concentration, C_{min}=Minimum Serum or Plasma Concentration, CsA=Cyclosporin A, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR= Not Reported, PSL=Prednisolone, RCT=Randomized Controlled Trial, T_{max}=Mean Time to Maximum Concentration, y=Years

Table 4. Studies showing that adverse events are not related to MMF dosage (continued)

Study	Population	Treatment	Major Findings/ Comments
Hubner[56] 2000 Study design: Case series Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 45y	Dose: 1.0 g BID Concomitant medications: Cyclosporine A Methylprednisolone	No significant difference was found in mean MMF dose between patients with adverse events and those without (1.77 vs. 1.90, p>0.05)
Kaplan[21] 1999 Study design: Case series Length of followup: >2 weeks	Organ transplanted: Kidney (Renal) Age: Range 46.7 +/- 9.2y for chronic renal subjects, 43.3 +/- 8.6y for renal patients without chronic insufficiency	Dose: 1.75 +/- 0.3 g/day Concomitant medications: Not reported	No p values were given, but there did not appear to be a relation between MMF dose and adverse events nor between MPA AUC and adverse events
Orlando[61] 2006 Study design: Case series Length of followup: mean 31.5 +/- 6.1 months	Organ transplanted: Liver Age: Mean 60.1y Range: 35 – 67y	Dose: 250 mg BID increased weekly by 500 mg to dose of 1500 mg/d Concomitant medications: Cyclosporine Tacrolimus	All adverse events occurred at MMF doses of 1.5 g except one case of (leukopenia and thrombocytopenia) which occurred at MMF 1 g.
Satoh[35] 2005 Study design: Prospective Cohort Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age:Mean AZA: 37.9 +/- 11.5y MMF: 44.3 +/- 11.6y	Dose: 1.0 – 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone	Neither MMF dose per bodyweight (34.0 vs. 32.8 mg/kg, respectively) nor MPA AUC_{0-12} (61.5 vs. 50.4 µg.h/mL, respectively) were significantly different in patients with viral infections compared to those without
Sugioka[76] 2006 Study design: Case series Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age: Range MPA group: 7 – 69y PSL group: 11 – 66y	Dose: MPA group: 1000 or 1500 mg/day Concomitant medications: Cyclosporine A Tacrolimus Prednisolone	No significant differences were observed in any pharmacokinetic parameter (AUC_{0-9}, C_{max}, T_{max}, predose concentration, dose, or dose/kg) between patients with and without adverse events of leucopenia or diarrhea

Table 4. Studies showing that adverse events are not related to MMF dosage (continued)

Study	Population	Treatment	Major Findings/ Comments
Takahashi[31] 1995 Study design: Non randomized controlled trial Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement ≥16y 1000 mg/d: Mean 37.7 +/- 6.3y 2000 mg/d: Mean 38.5 +/- 12.2 y 3000 mg/d: Mean 41.0 +/- 10.3 y	Dose: 1000, 2000, or 3000 mg/day Concomitant medications: Cyclosporine Steroids (no description)	The incidences of adverse events for the 1000 mg, 2000 mg, and 3000 mg MMF dose groups were: 25%, 10%, and 40%, respectively (p> 0.05)
van Besouw[72] 1999 Study design: Case series Length of followup: 8 months	Organ transplanted: Kidney (Renal) Age: NR	Dose: 2 g/d – 1 g/d Concomitant medications: Prednisone	MMF dose reduction from 2 g/day to 1.5 g/day did not increase hemoglobin concentration (p=0.12); however, after a further dose reduction to 1 g/day, the hemoglobin concentration in 20 out of 26 patients had reached pre-conversion (from CsA to MMF 0 concentrations (p=0.75). The authors summarized that “Not only the MMF dose but also the mycophenolic acid (MPA) predose concentration correlated with the Hb concentration”.
Wang[51] 1998 Study design: RCT Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 35-59y	Dose: Group 1. 1.0 g BID Group 2. 0.75 g BID Concomitant medications: Cyclosporine Corticosteroids Methylprednisolone Prednisone	No significant differences were observed in mean C_{max}, C_{min}, or AUC_{0-12} for patients in the MMF 1 g BID vs. 0.75 g BID groups. One patient in the MMF 1 g BID group and no patients in the 0.75 g BID group had an acute rejection epsiode. The authors also reported that “There were no obvious differences on MMF side effects between group 1 and group 2” but no data were given

Table 5. Association of MPA monitoring with free vs total MPA and albumin

Study	Associations
Atcheson[13] 2005	• Urea, creatinine correlate with free fractions of MPA, MPAG • Albumin correlate negatively with free fractions of MPA, MPAG • MPA, fMPA unrelated to rejection • fMPA AUC (but not total) higher with thrombocytopenia, leukopenia, infection than without
Borrows[14] 2006	• MPA concentrations correlate with anemia, leukopenia, diarrhea, viral infections • MPA concentrations inversely correlate with rejection within 1st month • hypoalbuminemia, renal impairment correlate with hemotoxicity • No association with MPA – platelets, bacterial infections • 1.60 mg/L MPA early post-transplant discriminates rejecters/non-rejecters • 2.75 mg/L MPA later post-transplant discriminates toxicity/no toxicity.
Cattaneo[18] 2001	• Creatinine, creatinine clearance correlates with MPA C_0 and AUC, renal function better with AUC > 40 • Free fraction MPA, not total, correaltes with RBC and leukocytes • No difference in rejections between AUC > or < 40
DeNofrio[19] 2000	• No difference in MPA C_0 between rejection grades • MPA AUC, fMPA AUC smaller in grade 2/3 vs. 0 or 1, no difference free vs. total • No significant difference MPA C0 between grade 2/3 vs. 0 or 1
Kaplan[21] 1999	•Free fraction, fMPA AUC, MPAG, but not MPA AUC increased in renal failure • Hint at increase of leukopenia (but not other adverse events.) with fMPA
Kuypers[15] 2003	• No relation MPA, fMPA, AcMPAG, MPAG – efficacy, adverse events • Intra-patient correlates AcMPAG, MPAG, AcMPAG/MPA – anemia • fMPA AUC, free fraction MPA, fMPA inverse correlation with GFR • AcMPAG AUC negative correlation with creatinine clearance (• fMPA AUC correlates with MPAG AUC)
Maes[16] 2003	• MPA, fMPA inverse correlation with colonic transit time, no difference free and total
Shaw[20] 2000	• MPA AUC, fMPA AUC, MPA, MPAG not associated with diarrhea • fMPA AUC higher in 5 patients with leukopenia and IRF than in 8 IRF patients without leukopenia (not significant) • MPA C_{-max}, AUC smaller in IRF vs. non-IRF on day 4, NS on day 90 • MPA clearance higher in IRF vs. non-IRF on day 4, NS on day 90 • No difference free fraction AUC in IRF vs non on days 4 and 90
Weber[17] 2002	• MPA AUC associated with rejection risk; 33.8 mg*h/L: 75% sensitivity, 64% specificity • MPA C_{12} 1.2 mg/L discriminates rejectors early post-tx, 83% sensitivity, 64% specificity • fMPA AUC, not MPA AUC, associated with leukopenia, infection • Albumin, GFR correlated with MPA AUC 1 wk post transplant, not later

Abbreviations: AcMPAG=Acyl Glucuronide Metabolite of Mycophenolic Acid AUC=Area-under-the-concentration-time curve, C_0=Predose Trough Blood Concentation, C_{max}=Maximum blood or Plasma Concentration fMPA=Free Mycophenolic Acid, GFR=Glomerular Filtration Rate, IRF=Impaired Renal Function, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, NS=Not Significant; RBC=Red Blood Cells

Table 6. Association of MPA outcomes with metabolites or genes

Study	Associations
Behrend[25] 1997	MPA, MPAG – renal function (MPA not correlation., MPAG inverse correlation., data not shown), AE/R (no association., data not shown)
Bunchman[23] 2001	MPA, MPAG – AE/R, No associations found, but data not shown
Cantin[58] 2002	MPA – rejection
Cattaneo[18] 2001	MPA – rejection, kidney function; fMPA, MPA – AE
Filler[73] 1998	MPA – diarrhea
Gajarski[44] 2004	MPA – rejection
Gonzalez-Roncero [109] 2005	MPA, fMPA, MPAG, C_0 and AUC – renal function: all higher in renal insufficiency than normal renal function, except MPA AUC
Johnson[111] 1999	MPA, MPAG AUC correlation - creatine; MPA AUC correlation – albumin
Kaplan[21] 1999	fMPA, MPAG AUC incr. in renal failure vs. function, MPA AUC same
Kuypers[15] 2003	MPA, metabolites – AE/R, lab outcomes Intra patient: No association MPA, fMPA, AcMPAG, MPAG C_0, C_{max}, AUC – rejection, diarrhea, leukopenia Higher AcMPAG C_0, MPAG C_0, AcMPAG/MPA, but not MPA in anemia (n=19) vs. not MPA, fMPA, MPAG, AcMPAG C_{max} or AUC: no difference between anemia (n=29) or leucopenia (n=12) or not Inter-patient: No association MPA, fMPA, AcMPAG, MPAG C_0, C_{max}, AUC – rejection, diarrhea, leukopenia, anemia (data not shown); diarrhea, rejection not captured by AUCs, C_{max} (too rare) Correlation with GFR: MPAG C_0: r^2 = -0.791 MPAG AUC: r^2 = -0.709 fMPA C_0: r^2 = -0.791 fMPA AUC: r^2 = -0.477 AcMPAG C_0: r^2 = -0.781 AcMPAG AUC: r^2 = -0.505 MPA C_0: r^2 = 0.399 MPA AUC: r^2= -0.039; all p<0.001
Maes[16] 2003	MPA, metabolites. – fecal fat loss Correlation fecal fat loss MPAG, AcMPAG, probably not MPA
Mandla R [38] 2006	MPA – rejection; fMPA – albumin, kidney function
Merkel U [22] 2005	Linear correlation. MPA C_0 – creatine, MPAG C_0 – creatine stronger correlation Slight linear correlation MPA – protein, not MPAG – protein Elevated transaminases (3 patients): MPA, MPAG concentrations similar to those without elevated transaminases Two CMV infections: MPA, MPAG in 1st patient similar to those in patients without CMV; MPA in second (reactivated chronic) CMV patient higher than in first CMV patient One diarrhea, no correlation to concentrations 4 rejections in 35 patients, 2 MPA concentrations in 2 acute rejections

Abbreviations: AcMPAG=Acyl Glucuronide Metabolite of Mycophenolic Acid, AE=Adverse Events, AE/R=Adverse/Rejection, AUC=Area-under-the-concentration-time curve, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, CMV=Cytomegalovirus, CyA=Cyclosporine, fMPA=Free Mycophenolic Acid, GFR=Glomerular Filtration Rate, IRF=Impaired Renal Function, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, ROC= Receiver Operating Characteristic, TAC=Tacrolimus

Table 6. Association of MPA outcomes with metabolites or genes (continued)

Study	Associations
Mogera[115] 1998	MPA, MPAG AUC inverse correlation – GFR
Morgera[116] 1998	MPAG AUC inverse correlation. - GFR, no difference for MPA
Naito[108] 2006	Positive correlation MPA, MPAG C_0 - creatine, stronger with CyA than Tac
Naesens[79] 2006	MPA – liver and renal function, genes; genes - AE/R (diarrhea)
Pawinski[64] 2006	MPA – rejection (ROC), renal function
Satoh[30] 2006	MPA – rejection, genes; genes - AE/R (diarrhea)
Shaw[20] 2000	MPA, fMPA, MPAG – diarrhea, renal function No association MPA, fMPA, MPAG – diarrhea MPAG, not MPA C_0 higher in IRF
Shaw[113] 1998	free fraction, MPAG, creatinine decrease with time, MPA increases but cannot be modeled
Sumethku[32] 2005	MPA – AE/R
Tsaroucha[24] 2000	MPA, MPAG – rejection (no correlation)
Weber[110] 1999	fMPA, MPAG AUC – GFR (inverse correlation), MPA AUC increases with time, fMPA, MPAG AUCs consistent
Weber[112] 1998	fMPA, MPAG, not MPA inverse correlation with GFR

Table 7. Studies showing some relationship between rejection and method of MPA monitoring

Study	Population	Treatment	Major Findings/ Comments
Armstrong[27] 2001 Study design: Case series Length of followup: 70 days	Organ transplanted: Kidney (Renal) Age: Inclusion requirement pediatric Mean NR	Dose: 600 mg/m^2 BID Concomitant medications: Cyclosporine Methylprednisolone	MPA AUC cut off of 29.5 mg.h/L (HPLC) for acute rejection had a diagnostic sensitivity of 66.7% and a diagnostic specificity of 79.4%.
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age:Inclusion requirement > 18y Range L: 47.8 +/- 11.5y; I: 46.9 +/- 13.8y; H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adjust; I: 0.95 g BID then adjust; H: 1.7 g BID then adjust Concomitant medications: Cyclosporine Corticosteroids	According to logistic regression analysis, MPA AUC values of 15, 25, and 40 mg.h/L are expected to yield 50%, 75%, and 90% of maximal achievable efficacy (with a 4% change in efficacy for every 1 mg.h/mL change in AUC at the midpoint of the logistic curve). Univariate logistic regression p values between biopsy-proven rejection vs. MPA AUC was < 0.0001. Note that the first 3 assessments were of full 12h AUCs whereas the later 6 assessments were of AUC_{0-12} (as predicted by LSS of C_0,C_{20min},C_{40min},C_{75min}, and C_{2h}).
Hazzan[28] 2005 Study design: RCT Length of followup: 1 year	Organ transplanted: Kidney (Renal) Age: Mean CsA 42.5 +/- 12.1 MMF 45.1 +/- 11.2	Dose: CsA group MMF dose = 1.93 +/- 0.2 g/day then withdrawn to 0, MMF group MMF dose = 1.99 +/- 0.1 g/day Concomitant medications: Cyclosporine Prednisone	MPA AUC (a 50 mg·h/L cut off), but not MPA predose concentration, was associated with risk for AR in multivariate analysis. Authors suggest that this cut off "needs to be confirmed by further investigations".
Lu[29] 2005 Study design: Non Randomized Clinical Trial Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 40.0 +/- 12.0y	Dose: mean 58.0 +/- 10.0 kg Concomitant medications: Cyclosporine Prednisone Tacrolimus	MPA AUC was lower in the patients with acute rejection compared to those without AR (40.93 vs. 53.88 µg·h/mL, p=0.038).
Mourad[33] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 32-68y Median 49y	Dose: 500mg BID + adjustment for side effects Concomitant medications: Tacrolimus Corticosteroids	MPA measurements at the time of acute rejection for 3 patients (5.8%) at a fixed dose of 500 mg twice daily were: MPA AUC of 37.7, 24.9, and 104.9 mg·h/L. (not much data)

Abbreviations: AR=Acute rejection, AUC=Area-under-the-concentration-time curve, BID=Twice Daily, C_0=Predose Trough Serum or Plasma Concentration, CsA=Cyclosporin A, EMIT=Enzyme-Multiplied Immunoassay Technique, ECMPS=Enteric Coated Mycophenolate Sodium, H=High, HPLC=High-Performance Liquid Chromatographic, I=Intermediate, L=Low, LSS=Limited Sampling Strategy, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not Reported, RCT=Randomized Controlled Trial, y=Years

Table 7. Studies showing some relationship between rejection and method of MPA monitoring (continued)

Study	Population	Treatment	Major Findings/ Comments
Satoh[30] 2006 Study design: Case series Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 41.2 +/- 2.1y Range 21 – 66y	Dose: 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Corticosteroids	Mean MPA AUC in patients with and without AR were 32.41 and 62.00 µg·h/L (daytime) and 24.44 and 57.88 µg·h/mL (nighttime), respectively ($p \leq 0.02$).
Sumethkul[32] 2005 Study design: Case series Length of followup: 3-8 months	Organ transplanted: Kidney (Renal) Age: Mean 39 +/- 9y	Dose: 720 mg BID Concomitant medications: Cyclosporine Prednisone	Only very weak inferential evidence as purpose of study was to assess delivery of MPA by ECMPS and not to correlate MPA measurements with health outcomes: 3 patients (MPA AUC = 52, 125, and 139 µg·h/L) had no evidence of rejection. 1 patients (MPA AUC = 52.3 µg·h/L) showed borderline acute rejection.
Takahashi[31] 1995 Study design: Non randomized controlled trial Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement ≥16y 1000 mg/d: Mean 37.7 +/- 6.3y 2000 mg/d: Mean 38.5 +/- 12.2y 3000 mg/d: Mean 41.0 +/- 10.3y	Dose: 1000, 2000, or 3000 mg/day Concomitant medications: Cyclosporine steroids (no description)	Rejection group 1: > 40 ug·h/mL MPA (1/12 patients); group 2: < 40 ug·h/mL MPA AUC (13/19 patients)
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2 - 16.0y	Dose: 600 mg/m2 twice a day to a maximum of 2 g/day Concomitant medications: Cyclosporine A Methylprednisolone	AUC was able to discriminate between patients with and without acute rejection. AUC (HPLC) of 33.8 mg·h/L had a diagnostic sensitivity of 80% and a diagnostic specificity of 57%; AUC (EMIT) was 36.1 mg·h/L.
Weber[17] 2001 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2-17.8y	Dose: 600 mg/m2 BSA twice a day up to 2 g/day maximum Concomitant medications: Cyclosporine A	MPA AUC was able to discriminate between patients with and without acute rejection. AUC (HPLC) of 33.8 mg·h/L had a diagnostic sensitivity of 75% and a diagnostic specificity of

Table 7. Studies showing some relationship between rejection and method of MPA monitoring (continued)

Study	Population	Treatment	Major Findings/ Comments
		Methylprednisolone	64.3%.
van Gelder[12] 1999 Study design: RCT Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range L: 47.8 +/- 11.5y; I: 46.9 +/- 13.8y; H: 50.6 +/- 10.5y	Dose: L: 16.1 ug hr/ml I: 32.2 ug hr/ml H: 60.6 ug hr/ml Concomitant medications: Cyclosporine Prednisone Corticosteroids	At the 3 target values for AUC (low-16.1; intermediate- 32.2; and high-60.6 mg.h/L, incidences of biopsy-proven acute rejection were 27.5%, 14.9%, and 11.5%, respectively (p=0.043). Note that all 3 target values were exceeded after day 21. There was a significant relation between median ln MPA AUC and biopsy-proven acute rejection (p<0.001).

Table 8. Studies showing some relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12})

Study	Population	Treatment	Major Findings/ Comments
Armstrong[27] 2001 Study design: Case series Length of followup: 70 days	Organ transplanted: Kidney (Renal) Age: NR	Dose: 600 mg/m^2 BID Concomitant medications: Cyclosporine Methylprednisolone Prednisone	MPA C_0 cut off was 1.0 mg/L (HPLC) for acute rejection had a diagnostic sensitivity of 77.8% and specificity of 64.5%; MPA C_0 cut off was 1.3 mg/L (EMIT)
Braun [39] 1998 Study design: Prospective Cohort Length of followup: median 280 days (19-585)	Organ transplanted: Kidney (Renal) Liver Age: NR	Dose: 30-40 mg/kg/day Concomitant medications: Tacrolimus	Weak supporting data: All 6 patients with liver graft rejection had low MPA predose concentrations (<1 mg/L)
Brusa[41] 2000 Study design: Prospective Cohort Length of followup: >12 months	Organ transplanted: Kidney (Renal) Age: Range for 18 patients 13-58y; 5 patients 35-56y	Dose: 250 to 1000 mg/day BID Concomitant medications: Cyclosporine Corticosteroids	Very weak supporting data for therapeutic drug monitoring: The authors reported "some episodes of interstitial rejection were observed in some transplanted patients having a predose concentration below 2 µg/mL" but no data were provided
Filler[46] 2000 Study design: Case series Length of followup: 6.2 +/- 2.7y (2.3-11.8)	Organ transplanted: Kidney (Renal) Age: Mean 17.2y +/- 4.2 SD y	Dose: 600 mg/m^2 BID Concomitant medications: Cyclosporine Steroids	Weak supportive data: Other than one patient with a very low MPA predose concentration (data not provided) who experienced a steroid-sensitive rejection episode 566 days after conversion to MMF, no patient experienced rejection
Gajarski[44] 2004 Study design: Case series Length of followup: NR	Organ transplanted: Heart (Cardiac) Age: Mean 15.4 +/- 9.5 years Range 1 month - 33 years	Dose: average 1206.8 +/- 301.9 mg/m^2 Concomitant medications: Cyclosporine Tacrolimus	Endomyocardial biopsy grade $\geq$ 2 were associated with significantly lower MPA predose concentrations (1.05 vs. 2.3, p<0.01) compared with grades 0, 1A or 1B. Grade $\geq$ 2 also occurred significantly more frequently with MPA concentrations < 2.5 µg/mL (p=0.03)

Abbreviations: AR=Acute rejection, AUC=Area-under-the-concentration-time curve, BID=Twice Daily, C_0=Predose Trough Serum or Plasma Concentration, CsA=Cyclosporin A, EMIT=Enzyme-Multiplied Immunoassay Technique, H=High, HPLC=High-Performance Liquid Chromatographic, I=Intermediate, L=Low, LSS=Limited Sampling Strategy, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not Reported, RCT=Randomized Controlled Trial, ROC=Receiver Operating Characteristic, RR=Relative Risk, TAC=Tacrolimus; TID=Three times per day; SD= Standard Deviation, y=Years

Table 8. Studies showing some relationship between rejection and method of MPA. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Hesse[45] 2001 Study design: Case series Length of followup: mean 10.1 months	Organ transplanted: Heart (Cardiac) Age: NR	Dose: 1500 mg BID + dose reductions on clinical symptoms Concomitant medications: Tacrolimus Prednisone CsA	Median MPA predose concentrations were significantly lower in patients with acute rejection compared to patients without acute rejection (1.36 vs. 1.76 mg/L, p=0.015)
Krumme[47] 1998 Study design: Case series Length of followup: 2 months	Organ transplanted: Kidney (Renal) Age: Range 46 +/-11y	Dose: 1 g BID Concomitant medications: Cyclosporine Methylprednisolone	Mean MPA predose (C_0 or trough) concentrations were significantly lower in patients with rejection compared with those without rejection (1.55 vs. 2.1, p<0.005)
Lu[48] 2006 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 34.1 +/- 7.1y Range 18 to 64y	Dose: weight directed dosage (50 kg: 2.0 g/day) starting 2 days before transplantation Concomitant medications: Cyclosporine CsA, Neoral steroids	Group A: n=239 (66.9%), no adverse events or acute rejections, mean MPA C_0 0.8416 +/- 0.1373 mg/L group B: n=100 (28.0%), adverse events, mean MPA C0 1.5903 +/- 0.3741 mg/L and group C: n=18 (5.0%), an acute rejection, mean MPA C_0 0.6057 +/- 0.2338 mg/L (p<0.001, =0.021, and <0.001, between A and B, A and C, and B and C, respectively. Although ROC curve analysis showed significant correlations between MPA C_0 and clinicial events (toxity and rejection), they did not reveal a high degree of diagnostic sensitivity (65.1 to 84.6%) or specificity (74.7 to 84.7%) according to the authors. Note that MPA C_0 and MPA AUC were not significantly correlated (r=0.325, p=0.411) in this study. Also note Lu[120] contains partial data (n=22); statistical significance same for both articles
Mandla[38] 2006 Study design: Non randomized controlled trial Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 54y Range 19 -77y	Dose: 1 g BID in combined kidney plus pancreas transplant patients 1 g TID Concomitant medications: Cyclosporine Tacrolimus Methylprednisolone Prednisone	Acute rejection rate was 44% in patients who attained > 1 µg/mL (i.e., the suggested minimum predose concentration) and 27% in those with concentrations < 1 µg/mL (p value not given); paradoxical finding suggests that CSA may confound the relation between MPA concentrations and AR

Table 8. Studies showing some relationship between rejection and method of MPA. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Meiser[7,8] 1999 Study design: Non randomized controlled trial Length of followup: Phase 1: 696 +/- 62d (606-790) Phase 2: 436 +/- 88d (175-562)	Organ transplanted: Heart (Cardiac) Age: Inclusion requirement Phase 1 & 2: >18y Range Phase 1: 50.6 +/- 11.4y (18-64); Phase 2: 54.1 +/- 8.9y (21-66)	Dose: 1 g BID Concomitant medications: Tacrolimus Prednisone Prednisolone	In Phase I, the mean MPA predose concentrations in patients who had no episodes of rejection, 1-2 rejection episodes, and 3 rejection episodes were: 3.6 vs. 2.2 vs. 1.4 µg/mL (p value not provided). In Phase 2, 3 patients (all of whom experienced only one rejection episode each) had MPA predose concentrations of 0.7, 1.3, and 0.9 µg/mL (although there were other confounding factors). The authors also suggested that mean MPA plasma concentrations > 3 µg/mL were not associated with rejection, but no details were provided
Mourad[33] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 32-68y Median 49y	Dose: 500 mg BID + adjustment for side effects Concomitant medications: Tacrolimus Corticosteroids	MPA measurements at the time of acute rejection for 3 patients (5.8%) at a fixed dose of 500 mg twice daily were: MPA C_0 of 1.86, 1.76, and 3.83 mg/L
Pawinski[43] 2006 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 48y Range 17 – 62y	Dose: 1 g BID Concomitant medications: Cyclosporine Tacrolimus Prednisone	C_0 cut off of 0.8 mg/L had a diagnostic sensitivity of 59.3% and diagnostic specificity of 83.3% (better than C_{max} but worse than AUC (based on LSS of C_0,$C_{0.5}$, and C_2)
Satoh[30] 2006 Study design: Case series Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 41.2 +/- 2.1y Range 21 – 66y	Dose: 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Corticosteroids	Mean MPA predose concentrations in patients with and without AR were 0.71 and 3.22 µg/mL (daytime) and 1.03 and 3.22 µg/mL (nighttime), respectively (p=0.001)
Tredger[40] 2004 Study design: Prospective Cohort Length of followup: 2 years (Feb 1 2000 - Feb 28 2002)	Organ transplanted: Liver Age: Mean adults median: 50.1y, children median: 3.5 years Range adults: 16.9 - 71.8y, children: 0.3 - 19.5y	Dose: adults: 500 mg BID then increased, children: 5 mg/kg BID then increased Concomitant medications: Cyclosporine Tacrolimus	Optimal efficacy and fewest complications in population at a predose MPA concentration around 1 mg/L. Figure 1b within this study shows the RR of rejection (95%CI) increased 4.2-fold (2.34-7.49), 2.5-fold (1.92-3.22) and 1.6-fold (1.28-2.03) at plasma MPA concentrations less than 0.5, 1.0 and 1.5 mg/L (p=0.003, 0.002 and 0.058).

Table 8. Studies showing some relationship between rejection and method of MPA. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2 - 16.0y	Dose: 600 mg/m^2 BID to a maximum of 2 g/day Concomitant medications: Cyclosporine Methylprednisolone	C_0 and C_{12} were able to discriminate between patients with and without acute rejection. C_{12} (HPLC) of 1.2 mg/L had a diagnostic sensitivity of 80% and a diagnostic specificity of 60%; C_{12} (EMIT) was 1.4 mg/L.
van Gelder[12] 1999 Study design: RCT Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range L: 47.8 +/- 11.5y; I: 46.9 +/- 13.8y; H: 50.6 +/- 10.5y	Dose: L: 16.1 µg hr/ml I: 32.2 µg hr/ml H: 60.6 ug hr/ml Concomitant medications: Cyclosporine Prednisone Corticosteroids	There was a significant relation between median ln C_0 and biopsy-proven acute rejection (p=0.01)
Yamani[42] 2000 Study design: Retrospective Cohort Length of followup: 179 +/- 52 days	Organ transplanted: Heart (Cardiac) Age: Mean 36 +/- 14y	Dose: 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	In the first year post-transplant, the incidence of rejection was significantly lower in the patient samples with MPA predose concentrations > 2 mg/L compared with those < 2 mg/L (8.8 vs. 14.9% at < 6 months, p=0.05 and 4.2 vs. 11.3% at 6-12 months, p=0.05). When CSA or TAC concentrations were "therapeutic", the incidence of rejection was significantly lower at MPA predose concentrations of $\geq$ 2 mg/L compared with those < 2 mg/L (3.6 vs. 14.4%, p=0.005)

Table 9. Studies showing some relationship between rejection and method of MPA monitoring. Limited sampling strategies - 2h Post (C_2)

Study	Population	Treatment	Major Findings/ Comments
Kiberd[57] 2004 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 48 +/- 13y	Dose: 2 g/day fixed Concomitant medications: Prednisone Neoral	Day 3 MPA C_2 significantly (p=0.025) predicted later rejection.

Abbreviations: MPA=Mycophenolic Acid, y=Years

Table 10. Studies showing some relationship between rejection and method of MPA. Limited sampling strategies - Other

Study	Population	Treatment	Major Findings/ Comments
DeNofrio[19] 2000 Study design: Case series Length of followup: 310 +/- 278 days	Organ transplanted: Heart (Cardiac) Age: Mean 53 +/- 10y	Dose: 1g BID Concomitant medications: Cyclosporine	Lower MPA AUC (as predicted by LSS of C_0,C_{20min},C_{40min},C_{75min}, and C_{120min}) was associated with cardiac allograft rejection. Specifically, MPA AUC values were significantly lower in patients with Grade 2/3 than in patients with Grade 1 rejection (26.1 vs. 51.7 mg·h/L, p< 0.05)
Kiberd[57] 2004 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age:Mean 48 +/- 13y	Dose: 2 g/day fixed Concomitant medications: Prednisone Neoral	Day 3 MPA AUC (based on LSS of C_0 ,C_1, C_2, and C_4) significantly predicted later rejection (p=0.007). The best cutoff point was an AUC concentration of 22 mg*h/L (sensitivity 82%, specificity 64%, negative predictive value 89% and positive predictive value 30%)
Kuriata-Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0 g/dayay Concomitant medications: Cyclosporine Prednisone	C_{40min} values were significantly lower in the patients with acute rejection compared with those without acute rejection (6.47 vs. 18.5 mg/L, p<0.05)
Le Meur[10] 2007 Study design: RCT Length of followup: 12 months	Organ transplanted: Kidney Age: Fixed dose group 49 +/- 13y Concentration-controlled group: 50 +/- 14y	Fixed dose group: 1g BID; Concentration-controlled group: Days 1-7, 1g BID, then dose to target AUC of 40 mg*h/L Concomitant medications: Cyclosporine Methylprednisolone Basiliximab Trimethoprim-sulfamethoxazole	Incidence of treatment failure, the primary study endpoint, was significantly lower in the concentration-controlled group (that used LSS of C_{20min}, C_1, and C_3 developed by Bayesian methods, to target an AUC of 40 mg*h/L) compared with the fixed dose group (29.2% vs. 47.7%, p=0.03); percentage of acute rejection (12.3% vs. 30.7%, p=0.01) and biopsy-proven acute rejection (7.7% vs. 24.6%) were also lower in the concentration-controlled group.
Okamoto[49] 2005 Study design: Non randomized controlled trial Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 38 +/- 14y	Dose: 25 mg/kg initially, then adjusted afterwards Concomitant medications: Cyclosporine n=35 Tacrolimus n=32	MPA AUC_{0-9} was significantly lower in patients with AR compared with those without (28.2 vs. 34.2 µg·h/mL, p=0.04085)

Abbreviations: AR=Acute rejection, AUC=Area-under-the-concentration-time curve, BID=Twice Daily, BSA=Body Surface Area, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, CsA=Cyclosporin A, LSS=Limited Sampling Strategy, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not Reported, RCT=Randomized Controlled Trial, y=Years

Table 10. Studies showing some relationship between rejection and method of MPA monitoring. Limited sampling strategies - Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Pawinski[64] 2006 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 17 – 62y	Dose: 0.5 - 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	AUC (based on LSS of C_0, $C_{0.5}$, and C_2) cut off for acute rejection of 27.5 mg·h/L had a diagnostic sensitivity of 81.2% and a diagnostic specificity of 93.4% (i.e., best predictor of acute rejection)
Pawinski[43] 2006 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 48y Range 17 – 62y	Dose: 1 g BID Concomitant medications: Cyclosporine Tacrolimus Prednisone	AUC (based on LSS of C_0, $C_{0.5}$, and C_2) cut off of 24.1 mg·h/L had a diagnostic sensitivity of 77.8% and diagnostic specificity of 91.7% (best compared with predose and C_{max})
Pillans[59] 2001 Study design: Case series Length of followup: 1 month	Organ transplanted: Kidney (Renal) Age: Range 21-65y	Dose: 2 g/day Concomitant medications: Cyclosporine Prednisone	MPA AUC (as predicted by a LSS of C_0, C_1, C_3, and C_6) was significantly lower in patients experiencing biopsy-proven rejection compared to those without rejection (27.6 vs. 35.1 mg·h/L, p=0.02). Four of 14 patients (29%) with an MPA AUC > 30 mg·h/L had a rejection episode but 8 of 13 patients (62%) with an MPA AUC <30 mg·h/L experienced a rejection
Weber[63] 2006 Study design: Case series Length of followup: 6 months post-transplant suspension trial: 36 months	Organ transplanted: Kidney (Renal) Age: Range German study: 3.17-16.0y, Suspension trial: 1.0-16.0y	Dose: German study: 600 mg/m^2 BSA up to 2 g/day suspension trial: 600 mg/m^2 body surface area BID (up to 1000 mg BID), corresponding to 1 g MMF BID in adult renal transplant recipients Concomitant medications: Cyclosporine CsA microemulsion: German study and suspension trial Methylprednisolone German study Prednisone suspension trial Corticosteroids	AUC (based on LSS of C_0, $C_{0.5}$, and C_2) was able to discriminate patients with acute rejection from those with no rejection; AUC cut off of 36.8 mg.h/L had prognostic sensitivity of 66.7% and prognostic specificity of 61.9%

Table 10. Studies showing some relationship between rejection and method of MPA monitoring. Limited sampling strategies - Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2-16.0y	Dose: 600 mg/m^2 BID to a maximum of 2 g/day Concomitant medications: Cyclosporine A Methylprednisolone	AUC (based on LSS of C_0, C_{75min}, and C_4) was able to discriminate between patients with and without acute rejection
Weber[17] 2001 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2-17.8y	Dose: 600 mg/m^2 BSA BID up to 2 g/day max Concomitant medications: Cyclosporine A Methylprednisolone	AUC (based on LSS of C_0, C_{75min}, and C_4) was able to discriminate between patients with and without acute rejection

Table 11. Studies showing no relationship between rejection and method of MPA monitoring

Study	Population	Treatment	Major Findings/ Comments
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study as [52] (Prospective Cohort) MPA AUC (56.5 vs. 46 mg.h/L, p=0.84) was not significantly lower between patients with later experienced acute rejection and those who did not. Incidence of acute rejection was numerically, but not significantly higher for patients who did not attain both target tacrolimus AUC of 150 ng.h/mL and MPA AUC of 45 mg.h/L by Day 7 compared with patients who did (26.3% vs. 7.7%, p=0.07). Note that a full AUC_{0-12} was obtained on Day 7, a 2-h AUC at week 6, and a 4-h AUC at months 3,6, and 12 (the 2- and 4-h AUCs were used to predict AUC_{0-12})
Mourad[37] 2000 Study design: Case series Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Mean 46y Range 33-57y	Dose: 1 g BID Concomitant medications: Cyclosporine Prednisolone	MPA AUC data were similar with 15.5, 72.7, and 42.1 ug *h/mL associated with rejection, adverse events, and uneventful outcomes, respectively (p value not provided)
Reggiani[34] 2001 Study design: RCT Length of followup: mean 31 +/- 7 months	Organ transplanted: Liver Age: Mean A: 49.7 +/- 4.6y, group B: 50.4 +/- 8.9y	Dose: 750 mg BID 1st month, 500 mg BID > 1 month Concomitant medications: Tacrolimusgroup A and B Methylprednisolone group B Prednisone group B	No difference in MPA AUC was observed in patients with acute rejection compared to those without (p value not provided)
Satoh[35] 2005 Study design: Prospective Cohort Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age: Mean AZA: 37.9 +/- 11.5y MMF: 44.3 +/- 11.6y	Dose: 1.0 – 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone	There was no significant difference in MPA AUC in patients with AR compared to those without AR (32.2 vs. 59.5 μg·h/L, p=0.081)

Abbreviations: AR=Acute rejection, AUC=Area-under-the-concentration-time curve, AZA=Azathioprine, BID=Twice Daily, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, RCT=Randomized Controlled Trial, y=Years

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12})

Study	Population	Treatment	Major Findings/ Comments
Barbari[53] 2005 Study design: Case control Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 39y Range 20 – 67y	Dose: 1 g BID range 1 - 2.5 g/day Concomitant medications: Cyclosporine Prednisone	There was a poor association between clinical events (primarily rejection, but also lymphocyte counts [an indicator of immune responsiveness]) and predose MPA concentrations. (r^2=0.0803 and 0.0577, respectively; Fig. 2, 3 and 4 , p. 357 in study)
Behrend [25] 1997 Study design: RCT Length of followup: at least 1 year	Organ transplanted: Kidney (Renal) Age: NR	Dose: 2 g/day or 3 g/day; dose per body weight was 22 to 54 mg/Kg; mean 83 mg/kg + - 8.4 body weight Concomitant medications: Cyclosporine Corticosteroids	Very very weak supportive data: The authors state that "there is no clearcut relationship between plasma concentrations and rejection, adverse events, and infections" but provide no data. Also, they state that interindividual variability in MPA predose (or C_0 or predose) concentrations is "by far greater than the correlation to …dose…" but do not provide specific data
Bilbao[62] 2006 Study design: Case series Length of followup: mean 39 + - 20 months; range 3 to 72 months	Organ transplanted: Liver Age: Mean 59 +/ - 6y	Dose: Initial dose of 500 mg/12h; reaching dose of 1 g each 12h for 2 weeks Concomitant medications: Cyclosporine Tacrolimus	The authors stated that "We have not found any correlation between MMF predose concentrations and the occurrence of rejections" but provided no data to substantiate this statement
Cantin[58] 2002 Study design: Case series Length of followup: 1 year	Organ transplanted: Heart (Cardiac) Age: Mean 54.4 +/- 14y Range 22–72y	Dose: Tac group: 1810 mg/day +/- 817, CsA group: 2447 +/- 896 Concomitant medications: Cyclosporine Tacrolimus Corticosteroids	No significant difference was observed in the incidence of overall rejection or high-grade rejection between patients with MPA predose concentrations < 2 mg/L and those with MPA concentrations $\geq$ 2 mg/L. However, both episodes of high grade (3A) rejection occurred in patients with MPA concentrations < 2 mg/L. The authors conclude that "There does not appear to be a benefit in continued monitoring of plasma mycophenolic acid concentrations beyond the first year of heart transplantation."

Abbreviations: AR=Acute rejection, ATG=Anti-Thymocyte Globulin, ATS=Anti-Tserum, AUC=Area-under-the-concentration-time curve, BID=Twice Daily, BSA=Body Surface Area, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, C_{min}=Minimum Serum or Plasma Concentration, CsA=Cyclosporin A, H=High, I=Intermediate, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not Reported, RCT=Randomized Controlled Trial, SIR=Sirolimus, TAC=Tacrolimus, y=Years

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
DeNofrio[19] 2000 Study design: Case series Length of followup: 310 +/- 278days	Organ transplanted: Heart (Cardiac) Age: Mean 53 +/- 10y	Dose: 1 g BID Concomitant medications: Cyclosporine	MPA C_0 in Grade 2/3 vs. Grade 0 rejection (0.65 vs. 1.20 mg/L, p=0.15)* *note that authors state these as positive findings, but they are actually not statistically significant
Dipchand[55] 2001 Study design: Retrospective Cohort Length of followup: 8 weeks	Organ transplanted: Heart (Cardiac) Age: Range 29days-23.5y Median 6.3y	Dose: various: 15-159 mg/kg Concomitant medications: Cyclosporine (A or neoral) Tacrolimus Corticosteroids azathiaprine ATG OKT3 (Monoclonal Antibody) ATS	A therapeutic predose MPA concentration was considered to be > 3 µg/mL. In the first 8 weeks post-transplant there were 7 rejection episodes in 6 patients with therapeutic concentrations and 4 patients with no rejection. There were 5 rejection episodes in 4 patients who had no therapeutic concentrations and 6 patients with no rejection. While the authors state “serum predose MPA concentrations may relate to efficacy”, this is not substantiated by these data
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18y Range: L: 47.8 +/- 11.5 y, I: 46.9 +/- 13.8y, H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adjusted I: 0.95 g BID then adjusted H: 1.7 g BID then adjusted Concomitant medications: Cyclosporine Corticosteroids	In bivariate logistic regression analysis, biopsy-proven rejection vs. MPA C_0 was not significant (p>0.05)
Hazzan[28] 2005 Study design: RCT Length of followup: 1 year	Organ transplanted: Kidney (Renal) Age: Mean CsA group 42.5 +/- 12.1y MMF group 45.1 +/- 11.2y	Dose: CsA group MMF dose = 1.93 +/- 0.2 g/day then withdrawn to 0, MMF group MMF dose = 1.99 +/- 0.1 g/day Concomitant medications: Cyclosporine Prednisone	MPA predose concentration was not associated with risk for AR in multivariate analysis, p>0.05

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Hesse[45] 2001 Study design: Case series Length of followup: Mean 10.1 months	Organ transplanted: Heart (Cardiac) Age: NR	Dose: 1500 mg BID + dose reductions on clinical symptoms Concomitant medications: Tacrolimus Prednisone CsA	There was no significant correlation between predose MPA concentrations and graft histology (endomyocardial biopsy scores). The authors state that they "do not find a significant correlation between MPA predose concentrations and the incidence of AR"
Hubner[56] 2000 Study design: Case series Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 45y	Dose: 1.0 g BID Concomitant medications: Cyclosporine A Methylprednisolone	Did not observe relation between predose concentration and rejection, but no rejection episodes occurred during MMF administration despite varying predose concentrations
Kiberd[57] 2004 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 48 +/- 13y	Dose: 2 g/day fixed Concomitant medications: Prednisone Neoral	Day 3 MPA C_0 did not significantly predicted later rejection (p=0.08)
Kuriata-Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0 g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed between patients with or without acute rejection within 3 months post-transplant in C_0. No significant difference was observed between patients with or without acute rejection during the 1-year followup.
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab (31 patients)	Same study as [52] (Prospective Cohort) Day 7 MPA C_0 (1.5 vs. 2.1 mg/L, p=0.90) was not significantly lower between patients with later experienced acute rejection and those who did not.

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Kuypers[52] 2003 Study design: Prospective Cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 51.5y	Dose: 1 g/day or 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Daclizumab (31 patients)	Same study as [36][Case series] Biopsy-proven acute rejection was not related to MPA C_0 (2.49 vs. 2.15 mg/L, rejection vs. no rejection, respectively; p=0.9). The time course of MPA exposure (i.e., AUC) was related more to MMF dose than to MPA predose concentrations. That is, MPA AUC increased by ~40% in the first 6 weeks post-transplant in the 2 g MMF group, but by only 17% in the 1g MMF group. At 3 months post-transplant, the 2-g group's MPA AUC declined minimally whereas the 1 g group's AUC decreased to its nadir. In both groups, MPA AUC returned to baseline values. Thus, the authors suggest that using MPA predose concentrations in routine therapeutic drug monitoring may be misleading regarding efficacy or toxicity
Kuypers[15] 2003 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 49.4 +/- 13.1y	Dose: 1 g BID Concomitant medications: Methylprednisolone Tacrolimus Daclizumab	Predose MPA concentrations (C_0) were not significantly different in patients with or without acute rejection or drug-related adverse events. The authors recommend that "A large randomized comparative trial examining the usefulness of frequent, more extensive pharmacokinetic measurements like area under the curve for MPA and its metabolites, is mandatory to answer the question."

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Kreis[50] 2000 Study design: RCT Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range SIR: 43.5 +/- 10.9y (22-62y); CsA: 42.9 +/- 11.4 y (18-60y)	Dose: 1 g BID Concomitant medications: Cyclosporine Corticosteroids Sirolimus	There was no significant difference in mean MPA predose concentrations between patients with and without acute rejection in either the concomitant sirolimus (3.06 vs. 3.48, p=0.50) or cyclosporine (1.71 vs. 2.20, p=0.39) group. Although the concentrations were higher, the small sample size limited statistical inference
Mourad[37] 2000 Study design: Case series Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Mean 46y Range 33-57y	Dose: 1 g BID Concomitant medications: Cyclosporine Prednisolone	Mean MPA predose concentrations were different for rejection vs. those experiencing MMF toxicity (1.3 vs. 3.1 mg/L, p<0.05); however, they were not significantly different for those experiencing rejection compared to those experiencing neither adverse events or rejection (1.3 vs. 2.2 mg/L, p>0.05)
Okamoto[49] 2005 Study design: Non randomized controlled trial Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 38 +/- 14y	Dose: 25 mg/kg initially, then adjusted Concomitant medications: Cyclosporine n=35 Tacrolimus n=32	MPA predose concentration was not significantly different in patients with and without AR
Orlando[61] 2006 Study design: Case series Length of followup: mean 31.5 + - 6.1 months	Organ transplanted: Liver Age: Mean 60.1y Range 35-67y	Dose: 250 mg per os BID increased weekly by 500 mg to dose of 1500 mg/day Concomitant medications: Cyclosporine Tacrolimus	Mean MPA predose (C_0 or trough) concentrations were not signficantly different between rejectors and non-rejectors (data provided in graphical form). Rejection episodes all occurred at “therapeutic” or “supratherapeutic” MPA predose concentrations (range of 1.5 to 7.2 mg/L)
Pillans[59] 2001 Study design: Case series Length of followup: 1 month	Organ transplanted: Kidney (Renal) Age: Range 21-65y	Dose: 2 g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed in MPA C_0 in patients with and without rejection

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Smak Gregoor[60] 2000 Study design: Case series Length of followup: 1 year	Organ transplanted: Kidney (Renal) Age: NR	Dose: 1 g BID, 750 mg BID, 500 mg BID Concomitant medications: Prednisone	No significant difference was observed between median MPA predose (C_0 or troughs) concentrations in 3 patients experiencing an acute rejection compared with the 24 patients who did not (2.3 vs. 3.8 mg/L), although patients with MPA predose concentrations > 3.5 mg/L did not experience rejection. Given the significant relation between MMF dose and MPA predose concentrations at 4 and 8 months (p=0.0002) and 12 months (p=0.01) and the lack of significant correlation with MPA predose concentrations and rejection, these results do not support routine monitoring of MPA predose concentrations
Tsaroucha[24] 2000 Study design: Prospective Cohort Length of followup: liver-165d; small bowel-58d; kidney-373d; all post transplant	Organ transplanted: Kidney (Renal) Liver Small bowel Age: Mean liver: 41.4 +/- 4.6y; small bowel: 18.7 +/- 3.9y; kidney: 44.3 +/- 2.7y	Dose: liver: 0.0258 g/kg/day small bowel: 0.0822 g/kg/day kidney: 0.0194 g/kg/day Concomitant medications: Tacrolimus Steroids	Mean MPA predose was not significantly different between the patients who experienced rejection and those who did not (0.95 vs. 1.06 mg/L, p=0.74)
Wang[51] 1998 Study design: RCT Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 35-59y	Dose: 1. 1.0 g BID 2. 0.75 g BID Concomitant medications: Cyclosporine Corticosteroids Prednisone Methylprednisolone	Very very weak supportive data: No significant differences were observed in mean C_{max}, C_{min}, or AUC_{0-12} for patients in the MMF 1 g BID vs. 0.75 g BID groups. One patient in the MMF 1 g BID group and no patients in the 0.75 g BID group had an acute rejection epsiode. The authors also reported that "There were no obvious differences on MMF side effects between group 1 and group 2" but no data were given

Table 12. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Weber[17] 2001 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2 - 17.8y	Dose: 600 mg/m^2 BSA BID up to 2 g/day max Concomitant medications: Cyclosporine A Methylprednisolone	MPA C_0 did not perform as well (p=0.07, respectively) in discriminating between rejectors and non-rejectors
Yamani[42] 2000 Study design: Retrospective Cohort Length of followup: 179 +/- 52 days	Organ transplanted: Heart (Cardiac) Age: Mean 36 +/- 14y	Dose: 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	There was no significant difference in incidence of rejection at >12 months in the patient samples with MPA predose concentrations > 2 mg/L compared with those < 2 mg/L (11.3 vs. 11.7%, p=0.92). There was also no significant difference in mean MMF predose concentrations between samples with and without rejection at any time post-transplant. When C_SA or TAC concentrations were “therapeutic”, the incidence of rejection was significantly lower at MPA predose concentrations of > 2 mg/L compared with those < 2 mg/L (3.6 vs. 14.4%, p=0.005), but when C_SA or TAC concentrations were “subtherapeutic”, there was no significant difference in incidence of rejection at MPA predose concentrations of > 2 mg/L vs. < 2 mg/L (15.4 vs. 13.9%, p>0.05)

Table 13. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies - 2h post (C_2)

Study	Population	Treatment	Major Findings/ Comments
Kuriata - Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0 g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed between patients with or without acute rejection within 3 months post-transplant in C_2. No significant difference was observed between patients with or without acute rejection during the 1-year followup in C_2

Table 14. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies - Other

Study	Population	Treatment	Major Findings/ Comments
Atcheson[13] 2004 Study design: Prospective Cohort Length of followup: 1 month	Organ transplanted: Kidney (Renal) Age: Mean 44.3 +/- 13.1y	Dose: 1 g BID =10 Concomitant medications: Cyclosporine n=32 Tacrolimus n=10 Simulect Diltiazem Prednisolone	MPA AUC (as predicted by LSS of C_0 ,C_1, C_3, C_6) was not significantly different between patients with and without biopsy-proven rejection (18.2 vs. 22.7 mg.h/L, p=0.25)
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18 y Range: L: 47.8 +/- 11.5 y, I: 46.9 +/- 13.8y, H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adjusted I: 0.95 g BID then adjusted H: 1.7 g BID then adjusted Concomitant medications: Cyclosporine Corticosteroids	Bivariate logistic regression between biopsy-proven rejection vs. MPA C_{max} was not significant
Kuriata - Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0 g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed between patients with or without acute rejection within 3 months post-transplant in C_{60min} or C_{max}. No significant difference was observed between patients with or without acute rejection during the 1 year followup in C_{60min} or C_{max}
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study as [52] (Prospective Cohort) MPA C_{max} (10.9 vs. 13 mg/L, p=0.46) was not significantly lower between patients with later experienced acute rejection and those who did not
Kuypers[52] 2003 Study design: Prospective Cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 51.5y	Dose: 1 g/day or 2 g/day Concomitant medications: Methylprednisolone Tacrolimus Daclizumab (31 patients)	Same study as [36] (Case Series) MPA C_{max} (10.95 vs. 13.0 mg/L; p=0.4) was not significantly different between patients with and without biopsy-proven rejection

Abbreviations: AUC=Area-under-the-concentration-time curve, Adj=adjust, BID=Twice Daily, BSA=Body Surface Area, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, H=High, I=Intermediate, L=Low, LSS=Limited Sampling Strategy, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, RCT=Randomized Controlled Trial, y=Years

Table 14. Studies showing no relationship between rejection and method of MPA monitoring. Limited sampling strategies- Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Mudge[65] 2004 Study design: RCT Length of followup: July 2002 - Feb 2003	Organ transplanted: Kidney (Renal) Age: Mean 45.2 +/- 13.2y	Dose: 1 g BID Concomitant medications: Cyclosporine Tacrolimus Prednisone	MPA AUC (as predicted by LSS of C_0, C_1, C_3, and C_6) was not significantly lower in individuals with rejection and those without (30.7 vs. 34 mg.h/L, p=0.40)
Wang[51] 1998 Study design: RCT Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 35-59y	Dose: 1. 1.0 g BID 2. 0.75 g BID Concomitant medications: Cyclosporine Corticosteroids Prednisone Methylprednisolone	Very very weak supportive data: No significant differences were observed in mean C_{max}, C_{min}, or AUC_{0-12} for patients in the MMF 1 g BID vs. 0.75 g BID groups. One patient in the MMF 1 g BID group and no patients in the 0.75 g BID group had an acute rejection epsiode. The authors also reported that "There were no obvious differences on MMF side effects between group 1 and group 2" but no data were given
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2-16.0y	Dose: 600 mg/m BID to a maximum of 2 g/day Concomitant medications: Cyclosporine A Methylprednisolone	C_{max} and AUC_{0-2} (i.e., C_0, C_{75min}, and C_4) did not perform as well (p=0.24 and p=0.06, respectively) in discriminating between rejectors and non-rejectors
Weber[17] 2001 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2-17.8y	Dose: 600 mg/m^2 BSA BID up to 2 g/day max Concomitant medications: Cyclosporine Methylprednisolone	C_{max} did not perform as well (p=0.10) in discriminating between rejectors and non-rejectors

Table 15. Studies showing some relationship between graft function or other efficacy parameter and method of MPA monitoring

Method of Monitoring	Study Author/Citation	Population	Treatment	Major Findings/ Comments
Full AUC (AUC_{0-12})	None	-	-	-
Limited sampling strategies – Predose (C_0, C_{min}, or C_{12})	Cattaneo[18] 2001 Study design: Case series Length of followup: 9 months	Organ transplanted: Kidney (Renal) Age: Mean AUC >40 µg.ml h: 31.9 +/- 9.0y, AUC <40 µg .ml h: 39 +/- 12.4y	Dose: 2 g/day Concomitant medications: Cyclosporine Prednisone Neurol	MPA C_0 was significantly and positively correlated with creatinine clearance (r=0.5, p< 0.01)
Limited sampling strategies - 2h Post (C_2)	None	-	-	-
Limited sampling strategies - Other	Cattaneo[18] 2001 Study design: Case series Length of followup: 9 months	Organ transplanted: Kidney (Renal) Age: Mean AUC >40 µg.ml h: 31.9 +/- 9.0y, AUC <40 µg.ml h: 39 +/- 12.4y	Dose: 2 g/day Concomitant medications: Cyclosporine Prednisone Neurol	MPA AUC (as predicted by C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min}) was significantly and positively correlated with creatinine clearance (r=0.52, p< 0.01)

Abbreviations: AUC=Area-under-the-concentration-time curve, C_0=Predose Trough Serum or Plasma Concentration, C_{min}=Minimum Serum or Plasma Concentration, H=high, MPA=Mycophenolic Acid

Table 16. Studies showing no relationship between graft function or other efficacy parameter and method of MPA monitoring

Method of Monitoring	Study	Population	Treatment	Major Findings/ Comments
Full AUC (AUC_{0-12})	Brunet[106] 2000 Study design: Case control Length of followup: 38.5 months (6-166 months)	Organ transplanted: Kidney (Renal) Age: Mean 42.5 +/- 13.6y Range 18-65y	Dose: 1 g, .075 g, and 0.5 g Concomitant medications: Prednisone CsA	Although the authors report that "for the majority of the patients an inverse relationship between MPA concentrations and IMPDH activity was observed", patients with comparable MPA AUC_{0-12} values exhibited different degrees of IMPDH inhibition (thus suggesting wide interindividual pharmacodynamic activity)
Limited sampling strategies – Predose (C_0, C_{min}, or C_{12})	Brunet[106] 2000 Study design: Case control Length of followup: 38.5 months (6-166 months)	Organ transplanted: Kidney (Renal) Age: Mean 42.5 +/- 13.6y Range 18-65y	Dose: 1 g, .075 g, and 0.5 g Concomitant medications: Prednisone CsA	Although the authors report that "for the majority of the patients an inverse relationship between MPA concentrations and IMPDH activity was observed", patients with comparable MPA predose concentrations exhibited different degrees of IMPDH inhibition (thus suggesting wide interindividual pharmacodynamic activity)
Limited sampling strategies - 2h Post (C_2)	None	-	-	-
Limited sampling strategies- Other	None	-	-	-

Abbreviations: AUC=Area-under-the-concentration-time curve, C_0=Predose Trough Serum or Plasma Concentration, C_{min}=Minimum Serum or Plasma Concentration, CsA=Cyclosporin A, IMPDH=Inosine 5'-Monophosphate Dehydrogenase, MPA=Mycophenolic Acid, y=Years

Table 17. Studies showing some relationship between adverse events and method of MPA monitoring

Study	Population	Treatment	Major Findings/ Comments
Filler[46] 2000 Study design: Case series Length of followup: 6.2 +/- 2.7 y (2.3-11.8)	Organ transplanted: Kidney (Renal) Age: Mean 17.2 +/- 4.2 SD y	Dose: 600 mg/m^2 BID Concomitant medications: Cyclosporine Steroids	Weak supportive data: Other than one patient with a high MPA AUC_{0-12} (data not provided) who experienced abdominal pain and diarrhea, no patient experienced adverse events
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study as [52] (Prospective Cohort) From 3 months on, patients with anemia or leuopenia had significantly higher MPA AUC compared with those without ($p \leq 0.04$). Note that a full AUC_{0-12} was obtained on Day 7, a 2-h AUC at week 6, and a 4-h AUC at months 3, 6, and 12 (the 2- and 4-h AUCs were used to predict AUC_{0-12})
Mourad[33] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 32-68y	Dose: 500 mg BID + adjustment for side effects Concomitant medications: Tacrolimus Corticosteroids	Significant differences were observed in AUC (48.38 vs. 36.04 mg·h/L, p=0.0006), and dose-normalized AUC (0.16 vs. 0.12 (mg·h/L)/(mg/m^2) between patients (samples) with side effects and those without. MPA AUC cut off of 37.6 mg·h/L for toxicity had a diagnostic sensitivity of 83.3% and a diagnostic specificity of 59.6%). ROC curves were not significantly different between these parameters
Takahashi[31] 1995 Study design: Non randomized controlled trial Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement ≥16y 1000 mg/day: Mean 37.7 +/- 6.3y 2000 mg/day: Mean 38.5 +/- 12.2y 3000 mg/day: Mean 41.0 +/- 10.3y	Dose: 1000, 2000, or 3000 mg/d Concomitant medications: Cyclosporine Steroids (no description)	Two patients (who had two of the 3 highest MPA AUC values of > 90 mg/h/L) developed CMV infection. Although other adverse events were reported, no attempts were made to relate them to MPA AUC

Abbreviations: AUC=Area-under-the-concentration-time curve, BID=Twice Daily, CMV=Cytomegalovirus, ROC= Receiver Operating Characteristic, MPA=Mycophenolic Acid SD=Standard Deviance, Y=years

Table 18. Studies showing some relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12})

Study	Population	Treatment	Major Findings/ Comments
Braun[39] 1998 Study design: Prospective Cohort Length of followup: median 280 d (19-585)	Organ transplanted: Kidney (Renal) Liver Age: Not reported	Dose: 30-40 mg/kg/day Concomitant medications: Tacrolimus	Weak supporting data: All 6 patients with liver graft rejection had low MPA predose concentrations (<1 mg/L) and severe diarrhea. Two renal transplant patients had relatively high MPA concentrations > 3 mg/L that "seemed to be associated with CMV infection" (but no data were provided)
Brusa[41] 2000 Study design: Prospective Cohort Length of followup: >12 months	Organ transplanted: Kidney (Renal) Age: Range 18 patients: 13-58y; 5 patients: 35-56y	Dose: 250 to 1000 mg/day BID Concomitant medications: Cyclosporine Corticosteroids	Very weak supporting data for therapeutic drug monitoring: Of 7 patients with MPA predose concentrations > 4 µg/mL, 3 had serious adverse events (thrombocytopenia, leucopenia, CMV and creatinemia)
Borrows[14] 2006 Study design: Case series Length of followup: 38 months median 25 months range 13-38 months	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 9y Range 37 – 55y	Dose: 750 mg – 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone	Median predose concentration of 2.6, 2.75. 2.40, and 3.20 mg/L best discrimated between patients with and without anemia, leucopenia, diarrhea, and viral infection, respectively
Borrows[69] 2005 Study design: Case series Length of followup: 30 months median 19 months range 6 – 30 months	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 9y Range 37-55y	Dose: 250-1500 mg/day corrected for body weight Concomitant medications: Tacrolimus Methylprednisolone Prednisone	Infective diarrhea was associated with lower MPA concentrations (p<0.001). MPA concentrations at onset of MMF-related diarrhea were higher than those of patients not experiencing diarrhea (3.1 mg/L vs. 2.0 mg/L, p<0.001)
Filler[73] 1998 Study design: Case series Length of followup: range 49 to 503 days, mean 282 days	Organ transplanted: Kidney (Renal) Age: Mean 15.8 +/- 1.6y Range 13 - 18 y	Dose: 600 mg/m^2 BID reduced to 320 mg/m^2/day over 7 weeks Concomitant medications: Tacrolimus Methylprednisolone	Except for one severe case of diarrhea, no patient developed diarrhea at an MPA predose concentration < 5 mg/L.

Abbreviations: AUC=Area-under-the-concentration-time curve, AZA=Azathioprine, BID=Twice Daily, C_0=Predose Trough Serum or Plasma Concentration, C_{min}=Minimum Serum or Plasma Concentration, CMV=Cytomegalovirus, CsA=Cyclosporin A, GI=Gastrointestinal, Hb=Haemoglobin, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR= Not Reported, RCT=Randomized Controlled Trial, ROC= Receiver Operating Characteristic, RR=Relative Risk, TAC=Tacrolimus, y=Years

Table 19. Studies showing some relationship between adverse events and method of MPA monitoring. Limited sampling strategies - 2h Post (C_2)

Study	Population	Treatment	Major Findings/ Comments
No studies addressed this question	-	-	-

Table 20. Studies showing some relationship between adverse events and method of MPA monitoring. Limited sampling strategies - Other

Study	Population	Treatment	Major Findings/ Comments
Brunet[66] 2006 Study design: Case series Length of followup: 6 months	Organ transplanted: Liver Age: Range 29 – 66y	Dose: 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	No significant correlation was found between adverse events and MPA C_0, Cmax, or AUC_{0-12}, except for patients w/ GI adverse events (diarrhea and/or nausea and vomiting) had higher C_{40min} than those without these side effects (22.9 mg/L vs. 7.4 mg/L, p=0.001)
Mourad[67] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 43y Range 16-67y	Dose: 1 g BID Concomitant medications: Cyclosporine Anti-thymocyte globulin	Of C_0, C_{30min}, and AUC, C_{30min} was the only significant discriminator between those with and without side effects (32.99 vs. 7.45 mg/L, p<0.0001). The authors speculated that the high MPA C_{30min} values (at a fixed 2 g/day MMF dose) may explain the occurrence of adverse events in patients with MPA AUCs within the "therapeutic range" and recommend that MMF daily oral dose be divided into more than two divided doses to prevent early toxicity
Mourad[33] 2001 Study design: Case series Length of study design: 3 months	Organ transplanted: Kidney (Renal) Age: Range 32-68y	Dose: 500 mg BID + adjustment for side effects Concomitant medications: Tacrolimus Corticosteroids	Significant differences were observed in C_{30min} (10.47 vs. 7.66 mg/L, p=0.0091) and C_{60min} (9.67 vs. 5.83 mg/L, p=-.0002) between patients (samples) with side effects and those without. MPA C_{60min} cut off of 8.09 mg/L for toxicity had a diagnostic sensitivity of 77.8% and a diagnostic specificity of 67.4%; ROC curves were not significantly different between C_0, C_{60min}, and AUC
Mudge[65] 2004 Study design: RCT Length of followup: July 2002 - Feb 2003	Organ transplanted: Kidney (Renal) Age: Mean 45.2 +/- 13.2y	Dose: 1 g BID Concomitant medications: Cyclosporine Tacrolimus Prednisone	Group w/toxicity: MPA AUC (as predicted by LSS of C_0, C_1, C_3, and C_6) = 39.3+-12.0 mg/h/L; Group w/o toxicity: 31.7+-7.9 mg/h/L p-value (gr. 1 vs gr. 2): $p < 0.05$; MPA AUC
Pillans[59] 2001 Study design: Case series Length of followup: 1 month	Organ transplanted: Kidney (Renal) Age: Range 21-65y	Dose: 2 g/day Concomitant medications: Cyclosporine Prednisone	Patients with GI adverse events (n=4) had significantly lower MPA AUC (as predicted by a LSS of C_0, C_1, C_3, and C_6) compared with patients without GI adverse events (23.7 vs. 33.2 mg.h/L, p=0.04). This paradoxical finding may suggest poor absorption and contribute to local GI effects. (Three of the 4 patients with GI adverse events also experienced acute rejection)

Abbreviations: AUC=Area-under-the-concentration-time curve, BID=Twice Daily, C_0=Predose Trough Serum or Plasma Concentration, GI=Gastrointestinal, LSS=Limited Sampling Strategy, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, RCT=Randomized Controlled Trial, ROC= Receiver Operating Characteristic, y=Years

Table 21. Studies showing no relationship between adverse events and method of MPA monitoring

Study	Population	Treatment	Major Findings/ Comments
Brunet[66] 2006 Study design: Case series Length of followup: 6 months	Organ transplanted: Liver Age: Range 29 – 66y	Dose: 1 g twice a day Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	No significant correlation was found between adverse events and AUC
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18 y Range: L: 47.8 +/- 11.5 y, I: 46.9 +/- 13.8y, H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adjusted I: 0.95 g BID then adjusted H: 1.7 g BID then adjusted Concomitant medications: Cyclosporine Corticosteroids	P value between each specified adverse event (diarrhea, nausea, leucopenia, CMV, urinary tract infection and abdominal pain) vs. MPA AUC was not significant (p>0.05). However, the risk of diarrhea and the risk of premature study withdrawal due to adverse events were both significantly related to mean MMF dose
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study as [52] (Prospective Cohort) MPA AUC was not significantly different in patients with and without infection. MPA AUC also was not significantly higher in patients with diarrhea compared with those without
Kuypers[52] 2003 Study design: Prospective Cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 1 g/day or 2 g/day Concomitant medications: Methylprednisolone Tacrolimus Daclizumab (32 patients)	same study as [36] (Case series) Diarrhea was not significantly related to MPA AUC
Lu[29] 2005 Study design: Non randomized Clinical Trial Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 40.0 +/- 12.0y	Dose: mean 58.0 +/- 10.0 kg Concomitant medications: Cyclosporine Prednisone Tacrolimus	There was no significant difference in rate of infection between patients with MPA AUC > 60 µg·h/mL vs. < 60 µg·h/mL.

Abbreviations: AUC=Area-under-the-concentration-time curve, AZA=Azathioprine, BID=Twice Daily, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, CMV=Cytomegalovirus, ECMPS=Enteric-Coated Mycophenolate Sodium, GI=Gastrointestinal, H=High, I=Intermediate, L=Low, LSS=Limited Sampling Strategy, MF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not Reported, RCT=Randomized Controlled Trial, y=Years

Table 21. Studies showing no relationship between adverse events and method of MPA monitoring (continued)

Study	Population	Treatment	Major Findings/ Comments
Mourad[67] 2001 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 43y Range 16-67y	Dose: 1 g BID Concomitant medications: Cyclosporine Anti-thymocyte globulin	Mean MPA AUC was significantly higher in patients who experienced adverse events compared to those with uneventful outcomes (52.1 vs. 39.8 mg·h/L, p=0.0005). AUC was not a significant discriminator between those with and without side effects
Mourad[37] 2000 Study design: Case series Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Mean 46y Range 33-57y	Dose: 1 g BID Concomitant medications: Cyclosporine Prednisolone	Mean MPA predose concentrations were not significantly different for those experiencing MMF toxicity (3.1 vs. 2.2 mg/L, p>0.05) compared to those experiencing neither rejection nor adverse events. MPA AUC data were similar with 15.5, 72.7, and 42.1 mg·h/L associated with rejection, MMF toxicity, and neither rejection nor adverse events, respectively (p value not provided)
Satoh[35] 2005 Study design: Prospective Cohort Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age: Mean AZA: 37.9 +/- 11.5y MMF: 44.3 +/- 11.6y	Dose: 1.0 – 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone	MPA AUC was not significantly different in patients with viral infections compared to those without (61.5 vs. 50.4 µg·h/mL, respectively)
Sumethkul[32] 2005 Study design: Case series Length of followup: 3-8 months	Organ transplanted: Kidney (Renal) Age: Mean 39 +/- 9y	Dose: 720 mg BID Concomitant medications: Cyclosporine Prednisone	Only very weak inferential evidence as purpose of study was to assess delivery of MPA by ECMPS and not to correlate MPA measurements with health outcomes: 2 patients with a AUC_{0-12} for MPA 31 and 125 mg·h/L had less diarrhea and 1 patient needed reduction of ECMPS dosage

Table 21. Studies showing no relationship between adverse events and method of MPA monitoring (continued)

Study	Population	Treatment	Major Findings/ Comments
van Gelder[12] 1999 Study design: RCT Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range L: 47.8 +/- 11.5y; I: 46.9 +/- 13.8y; H: 50.6 +/- 10.5y	Dose: L: 16.1 ug hr/ml I: 32.2 ug hr/ml H: 60.6 ug hr/ml Concomitant medications: Cyclosporine Prednisone Corticosteroids	The relation between premature study withdrawal due to adverse events and median ln MPA AUC was not statistically significant (p=0.434). Posthoc analysis showed that only the premature withdrawal due to GI (and not other) adverse events was significantly related to MMF dose. This suggests that high local, non-systemic, drug concentrations, may be responsible for the GI adverse events. The authors clarify that statistical significance is lost when only the first 3 predose concentrations are used in the logistic regression analysis and thus caution against making dosage adjustments on a limited number of predose concentrations. Note that the first 3 assessments were of full 12h AUCs whereas the later 6 assessments were of $AUC_{0\text{-}12}$ (as predicted by LSS of C_0, C_{20min}, C_{40min}, $C_{75min,2h}$)
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2 - 16.0y	Dose: 600 mg/m^2 BID to a maximum of 2 g/day Concomitant medications: Cyclosporine A Methylprednisolone	There was no significant association between AUC and incidence of adverse events (leucopenia, infections, diarrhea, anemia, or thrombocytopenia)
Weber[17] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2 - 17.8y	Dose: 600 mg/m^2 BID up to 2 g/day max Concomitant medications: Cyclosporine A Methylprednisolone	There was no significant association between AUC and incidence of adverse events (leucopenia, infections, diarrhea, vomiting, or abdominal pain).[Note that free MPA C_{max} and free MPA AUC were able to discriminate between patients with or without infections and/or leukemia]

Table 22. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12})

Study	Population	Treatment	Major Findings/ Comments
Behrend[25] 1997 Study design: RCT Length of followup: at least 1 year	Organ transplanted: Kidney (Renal) Age: Not reported	Dose: 2 g/day or 3 g/day; dose per body weight was 22 to 54 mg/Kg; mean 83 mg/kg + - 8.4 body weight Concomitant medications: Cyclosporine Corticosteroids	Very very weak supportive data: The authors state that "there is no clearcut relationship between plasma concentrations and rejection, adverse events, and infections" but provide no data. Also, they state that interindividual variability in MPA predose (or C_0 or predose) concentrations is "by far greater than the correlation to …dose…" but do not provide specific data
Bilbao[62] 2006 Study design: Case series Length of followup: mean 39 + - 20 months; range 3 to 72 months.	Organ transplanted: Liver Age:Mean 59 +/- 6y	Dose: Initial dose of 500 mg/12h; reaching dose of 1 g each 12h for 2 weeks. Concomitant medications: Cyclosporine (neoral) Tacrolimus	Although adverse events (leukopenia, diarrhea) were reported, no attempts were made to relate these to MPA predose (or C_0 or predose) concentrations.Dose adjustments were based on tolerability and adverse events and not on predose concentrations although they "tried to avoid concentrations over 4 ng/mL"
Borrows[14] 2006 Study design: Case series Length of followup: minimum of 12 months median 25 months range 13-38 months	Organ transplanted: Kidney (Renal) Age: Mean 46 +/- 9y Range 37–55y	Dose: 750 mg – 2 g/day Concomitant medications: Tacrolimus Methylprednisolone Prednisone Corticosteroids Ganciclovir (3 months) Co-Trimoxazole (6 months) Isoniazid and pyridoxine (Indo-Asians and those with previous TB) Basilizimab or Daclizumab (79 patients)	No association was seen between MPA concentration and platelet count. No association was seen between MPA concentration and the development of bacterial infection

Abbreviations: AUC=Area-under-the-concentration-time curve, BID=Twice Daily, BSA=Body Surface Area, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, CMV=Cytomegalovirus, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, NR=Not Reported, PSL=Predonisolone, RCT=Randomized Controlled Trial, TB=Tuberculosis, y=Years

Table 22. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Brunet[66] 2006 Study design: Case series Length of followup: 6 months	Organ transplanted: Liver Age: Range 29–66y	Dose: 1 g twice a day Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	No significant correlation was found between adverse events and MPA C_0
Cattaneo[18] 2001 Study design: Case series Length of followup: 9months	Organ transplanted: Kidney (Renal) Age: Mean AUC>40 ug·ml h: 31.9 +/- 9.0y AUC<40 ug·ml h: 39 +/- 12.4y; Range 19-61y	Dose: 2 g/day Concomitant medications: Cyclosporine Prednisone CSA Neoral	Total MPA predose concentration did not correlate significantly with red blood cell or leukocyte count (but free MPA fraction correlated negatively and significantly)
Deierhoi[75] 1993 Study design: RCT Length of followup: phase I trial: mean 26 months range 22 - 28 months rescue: mean 20 months range 16 - 24 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement phase I: older than 18y, rescue: older than 16y	Dose: phase I: 1500 - 3000 mg/day rescue: 2000 mg/day and 3000-3500 mg/day if no response in first week to 2000 mg Concomitant medications: Phase I: Minnesota antilymphocyte globulin(MALG) Prednisone Methylprednisolone Cyclosporine Rescue: Corticosteroids Cyclosporine	Authors stated that “there was no clear cut correlation between serum concentrations [C_{max} and trough] and the occurrence of side effects or rejection episodes”, but no data were given
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18y Range: L: 47.8 +/- 11.5 y, I: 46.9 +/- 13.8y, H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adjusted I: 0.95 g BID then adjusted H: 1.7g BID then adjusted Concomitant medications: Cyclosporine Corticosteroids	P values between each specified adverse event (diarrhea, nausea, CMV, urinary tract infection and abdominal pain) vs. MPA C_0 was not significant ($p>0.05$)

Table 22. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Kuriata - Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0 g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed between patients with or without leucopenia during the 1 year followup in C_0
Okamoto[49] 2005 Study design: Non randomized controlled trial Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 38 +/- 14 y	Dose: 25 mg/kg initially, then adjusted afterwards Concomitant medications: Cyclosporine n=35 Tacrolimusn=32	MPA predose concentration was not significantly different in patients with and without adverse events
Kiberd[57] 2004 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age:Mean 48 +/- 13y	Dose: 2 g/day fixed Concomitant medications: Prednisone Neoral	MPA C_0, did not significantly predict toxicity (p=0.90)
Krumme[47] 1998 Study design: Case series Length of followup: 2 months	Organ transplanted: Kidney (Renal) Age: Range 46 +/-11y	Dose: 1 g BID Concomitant medications: Cyclosporine Methylprednisolone	Incidences of CMV infection and urinary tract infection were not significantly different in patients with and without rejection, but no data were provided on a relation between MPA predose concentrations and adverse events
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study as [52] (Prospective Cohort) MPA C_0 was not significantly higher in patients with diarrhea compared with those without
Kuypers[15] 2003 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 49.4 +/- 13.1y	Dose: 1 g BID Concomitant medications: Methylprednisolone Tacrolimus Daclizumab	Predose MPA concentrations (C_0) were not significantly different in patients with or without drug-related adverse events. The authors recommend that "A large randomized comparative trial examining the usefulness of frequent, more extensive pharmacokinetic measurements like area under the curve for MPA and its metabolites, is mandatory to answer the question of the necessity for routine therapeutic drug monitoring for mycophenolate mofetil in renal transplantation."

Table 22. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Kuypers[52] 2003 Study design: Prospective Cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 51.5y	Dose: 1 g/day or 2 g/day Concomitant medications: Methylprednisolone Tacrolimus Daclizumab (31 patients)	Same study as [36] (Case series) Diarrhea was not significantly related to MPA C_0. The time course of MPA exposure (i.e., AUC_{0-12}) was related more to MMF dose than to MPA predose concentrations. That is, MPA AUC_{0-12} increased by ~40% in the first 6 weeks post-transplant in the 2-g MMF group, but by only 17% in the 1-g MMF group. At 3 months post-transplant, the 2-g group's MPA AUC_{0-12} declined minimally whereas the 1-g group's AUC_{0-12} decreased to its nadir. In both groups, MPA AUC_{0-12} returned to baseline values. Thus, the authors suggest that using MPA predose concentrations in routine therapeutic drug monitoring may be misleading regarding efficacy or toxicity
Merkel[22] 2005 Study design: Retrospective Cohort Length of followup: 16 months, mean 5.7 months	Organ transplanted: Kidney (Renal) Age: Mean 44 +/- 13.6y Range 13–63y	Dose: 0.5 - 1.0 g BID Concomitant medications: Cyclosporine Prednisone Corticosteroids	There was no correlation between hemoglobin concentrations and MPA predose concentration (p value not provided)
Mourad[67] 2001 Study design:v Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 43y Range 16-67y	Dose: 1 g BID Concomitant medications: Cyclosporine Anti-thymocyte globulin Steroids	There was no significant difference (p-0.0635) in mean MPA C_0 (predose or trough) between those with adverse events and those without. C_0 was nor a significant discriminator between those with and without side effects
Mourad[37] 2000 Study design: Case series Length of followup: 12 weeks	Organ transplanted: Kidney (Renal) Age: Mean 46y Range 33-57y	Dose: 1g BID Concomitant medications: Cyclosporine Prednisolone	Mean MPA predose concentrations were not significantly different for those experiencing MMF toxicity (3.1 vs. 2.2 mg/L, p>0.05) compared to those experiencing neither rejection nor adverse events. MPA AUC data were similar with 15.5, 72.7, and 42.1 mg·h/L associated with rejection, MMF toxicity, and neither rejection nor adverse events, respectively (p value not provided)

Table 22. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Pawinski[64] 2006 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 17–62y	Dose: 0.5 - 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	No correlation was found between MPA predose and wbc count or hematocrit values
Shaw[20] 2000 Study design: Prospective Cohort Length of followup: 90 days	Organ transplanted: Kidney (Renal) Age: Range 47 +/-9.7y	Dose: 1 g BID Concomitant medications: Neoral Steriods	Weak supportive data: The authors stated "The occurrence of diarrhea was not associated with high concentrations of either total or free MPA AUC, predose, or MPAG predose values", but did not provide specific data
Sugioka[76] 2006 Study design: Case series Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age: Range MPA group: 7 - 69y, PSL group: 11 - 66y	Dose: MPA group: 250 or 1750 mg/day Concomitant medications: Cyclosporine Tacrolimus	No significant differences were observed in predose concentration between patients with and without adverse events of or diarrhea
van Besouw[72] 1999 Study design: Case series Length of followup: 8 months	Organ transplanted: Kidney (Renal) Age: Not reported	Dose: 2 g/day – 1 g/day Concomitant medications: Prednisone	MPA predose concentration was not correlated with the leukocyte counts (Spearman r= - 0.13, p=0.27)
van Gelder[12] 1999 Study design: RCT Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range L: 47.8 +/- 11.5y; I: 46.9 +/- 13.8y; H: 50.6 +/- 10.5y	Dose: L: 16.1 ug hr/ml I: 32.2 ug hr/ml H: 60.6 ug hr/ml Concomitant medications: Cyclosporine Prednisone Corticosteroids	The relation between premature study withdrawal due to adverse events and median ln C_0 was not statistically significant (p=0.512)
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2 - 16.0y	Dose: 600 mg/m^2 twice a day to a maximum of 2 g/day Concomitant medications: Cyclosporine A Methylprednisolone	There was no significant association between C_0 and incidence of adverse events (leucopenia, infections, diarrhea, anemia, or thrombocytopenia)

Table 22. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Predose (C_0, C_{min}, or C_{12}) (continued)

Study	Population	Treatment	Major Findings/ Comments
Weber[17] 2001 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2 - 17.8y	Dose: 600 mg/m^2 BSA twice a day up to 2 g/day max Concomitant medications: Cyclosporine A Methylprednisolone	There was no significant association between C_0 and incidence of adverse events (leucopenia, infections, diarrhea, vomiting, or abdominal pain)
Yamani[42] 2000 Study design: Retrospective Cohort Length of followup: 179 +/- 52 days	Organ transplanted: Heart (Cardiac) Age: Mean 36 +/- 14y	Dose: 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	There was no significant difference in mean total white blood cell count, total lymphocyte count, or percentage lymphocytes in MPA predose concentration groups of < 2, 2-5, and > 4 mg/L)

Table 23. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – 2h Post (C_2)

Study	Population	Treatment	Major Findings/ Comments
Kiberd[57] 2004 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 48 +/- 13y	Dose: 2 g/day fixed Concomitant medications: Prednisone Neoral	MPA C_2 did not significantly predict toxicity (p=0.90)
Kuriata - Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0 g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed between patients with or without during the 1-year followup in C_2

Abbreviations: MPA=Mycophenolic Acid, y=Years

Table 24. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies - Other

Study	Population	Treatment	Major Findings/ Comments
Atcheson[13] 2004 Study design: Prospective Cohort Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 44.3 +/- 13.1 y	Dose: 1 g BID Concomitant medications: Cyclosporine n=32 Tacrolimus n=10 Simulect Diltiazem Prednisolone	Patients who experienced one or more hematological adverse events (thrombocytopenia, leucopenia, or infection) did not have significantly higher MPA AUC_{0-6} (i.e., C_0, C_1, C_3, and C_6) values compared to patients without these adverse events (p=0.18). The latter may suggest that MPA's GI adverse events may be related to local drug concentrations. (Note that free MPA AUC was a better predictor of hematological or infectious adverse events compared with total MPA AUC.)
Brunet[66] 2006 Study design: Case series Length of followup: 6 months	Organ transplanted: Liver Age: Range 29 – 66y	Dose: 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	No significant correlation was found between adverse events and MPA C_{max} except for patients w/ GI adverse events (diarrhea and/or nausea and vomiting)
Deierhoi[75] 1993 Study design: RCT Length of followup: phase I trial: mean 26 months range 22 - 28 months rescue: mean 20 months range 16 - 24 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement phase I: older than 18y, rescue: older than 16y	Dose: phase I: 1500 - 3000 mg/day rescue: 2000 mg/day and 3000-3500 mg/day if no response in first week to 2000 mg Concomitant medications: Phase I: Minnesota antilymphocyte globulin(MALG) Prednisone Methylprednisolone Cyclosporine Rescue: Corticosteroids Cyclosporine	Authors stated that "there was no clear cut correlation between serum levels [C_{max} and trough] and the occurrence of side effects or rejection episodes", but no data were given

Abbreviations: AUC=Area-under-the-concentration-time curve, BID=Twice Daily, BSA=Body Surface Area, C_0=Predose Trough Serum or Plasma Concentration, C_{max}=Maximum Serum or Plasma Concentration, CMV=Cytomegalovirus, GI=Gastrointestinal, LSS=Limited Sampling Strategy, LSS=Limited Sampling Strategy, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, MPA=Mycophenolic Acid, NR= Not Reported, PSL=Prednisolone, RCT=Randomized Controlled Trial, WBC=White Blood Cells, y=Years

Table 24. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Hale[11] 1998 Study design: RCT Length of followup: 20 weeks	Organ transplanted: Kidney (Renal) Age: Inclusion requirement > 18 y Range: L: 47.8 +/- 11.5 y, I: 46.9 +/- 13.8y, H: 50.6 +/- 10.5y	Dose: L: 0.45 g BID then adjusted I: 0.95 g BID then adjusted H: 1.7 g BID then adjusted Concomitant medications: Cyclosporine Corticosteroids	P values between each specified adverse event (diarrhea, nausea, , CMV, urinary tract infection and abdominal pain) vs. Cmax was not significant (p>0.05)
Heller[77] 2007 Study design: Prospective cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 53.4y	Dose: Fixed dose group: 1 g BID, Concentration-controlled group: target concentration of 30-60 mg*h/L Concomitant medications: Cyclosporine Tacrolimus	MPA AUC, as predicted by LSS of C_0, $C_{0.5}$, and C_2, was not significantly different between patients who suffered an episoide of diarrhea versus those who did not.
Kaplan[21] 1999 Study design: Case series Length of followup: >2 weeks	Organ transplanted: Kidney (Renal) Age: Range chronic renal subjects 46.7 +/- 9.2y; renal patients without chronic insufficiency 43.3 +/- 8/6y	Dose: 1.75 +/- 0.3 g/day Concomitant medications: Not reported	No p values were given, but there did not appear to be a relation between MMF dose and adverse events nor between MPA AUC and adverse events. MPA AUC was predicted by LSS of C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min}. [Leucopenia occurred in 4 patients, 3 of whom had the highest free MPA AUC values (5.07, 2.26, and 1.92 µg.h/mL) and one who had the fifth highest free MPA AUC (1.69 µg.h/mL); a patient with the 4th highest free MPA AUC (1.82 µg.h/mL) did not experience . Abdominal pain, diarrhea and CMV occurrences were infrequent and thus could not be correlated to free MPA AUC.]
Kiberd[57] 2004 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Mean 48 +/- 1 3y	Dose: 2 g/day fixed Concomitant medications: Prednisone Neoral	MPA AUC, as predicted by LSS of C_0, C_1, C_2, and C_4, did not significantly predict toxicity (p=0.29)

Table 24. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Kuriata-Kordek[54] 2002 Study design: Case control Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Inclusion requirement group I: 38.12 +/- 9.5y, group II: 38.52 +/- 9.21y	Dose: 2.0g/day Concomitant medications: Cyclosporine Prednisone	No significant difference was observed between patients with or without during the 1 year followup in C_{40min}, C_{60min}, or C_{max}
Kuypers[36] 2004 Study design: Case series Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Median 51.5y	Dose: 0.5 g BID or 1 g BID Concomitant medications: Tacrolimus Methylprednisolone Daclizumab	Same study as Kuypers[52] (Prospective Cohort) MPA C_{max} was not significantly higher in patients with diarrhea compared with those without
Kuypers[52] 2003 Study design: Prospective Cohort Length of followup: 12 months	Organ transplanted: Kidney (Renal) Age: Mean 51.5y	Dose: 1 g/day or 2 g/day Concomitant medications: Methylprednisolone Tacrolimus Davlizumab (31 patients)	Same study as Kuypers[36] (Case series) Diarrhea was also not significantly related to MPA C_{max}
Le Meur[10] 2007-10-30 Study design: RCT Length of followup: 12 months	Organ transplanted: Kidney Age: Fixed dose group 49 +/- 13y Concentration-controlled group: 50 +/- 14y	Fixed dose group: 1 g BID; Concentration-controlled group: Days 1-7, 1 g BID, then dose to target AUC of 40 mg*h/L Concomitant medications: Cyclosporine Methylprednisolone Basiliximab Trimethoprim-sulfamethoxazole	There was no significant difference ($p>0.05$) in incidence of adverse events (total, gastrointestinal events, anemia, leucopenia, general infections, cytomegalovirus, other viral infections, bacterial infections, or other infections) between the concentration-controlled and fixed dose groups, except for herpes infections which occurred more frequently in the concentration-controlled group (8 vs. 1 event, $p<0.05$). Overall, 97% and 90% of patients in the concentration-controlled and fixed dose groups, respectively, reported one (or more) adverse events.
Okamoto[49] 2005 Study design: Non randomized controlled trial Length of followup: NR	Organ transplanted: Kidney (Renal) Age: Mean 38 +/- 14 years	Dose: 25 mg/kg initially, then adjusted afterwards Concomitant medications: Cyclosporine n=35 Tacrolimus n=32	MPA AUC_{0-9} was not significantly different in patients with and without adverse effect

Table 24. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Pawinski[64] 2006 Study design: Case series Length of followup: 3 months	Organ transplanted: Kidney (Renal) Age: Range 17–62y	Dose: 0.5 - 2 g/day Concomitant medications: Cyclosporine Tacrolimus Prednisone	No correlation was found between MPA AUC (as predicted by LSS of C_0, $C_{0.5}$, and C_2) and wbc count or hematocrit values
Shaw[20] 2000 Study design: Prospective Cohort Length of followup: 90 days	Organ transplanted: Kidney (Renal) Age: Range 47 +/-9.7y	Dose: 1 g BID Concomitant medications: Neoral Steriods	Weak supportive data: The authors stated "The occurrence of diarrhea was not associated with high concentrations of either total or free MPA AUC, predose, or MPAG predose values", but did not provide specific data. (They also reported a 21% higher than average *free* MPA AUC in patients who had leucopenia compared with those who did not.]) MPA AUC was predicted by LSS of C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min}.
Sugioka[76] 2006 Study design: Case series Length of followup: 28 days	Organ transplanted: Kidney (Renal) Age: Range MPA group: 7-69y, PSL group: 11-66y	Dose: MPA group: 250 or 1750 mg/day Concomitant medications: Cyclosporine A Tacrolimus Prednisone	No significant differences were observed in AUC_{0-9} (i.e., C_0, C_1, C_2, C_3, C_4, C_6, and C_9) or Cmax, between patients with and without adverse events of leucopenia or diarrhea
Weber[26] 2002 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Mean 11.8y Range 3.2-6.0y	Dose: 600 mg/m^2 BID to a maximum of 2 g/day Concomitant medications: Cyclosporine A Methylprednisolone	There was no significant association between C_{max}, AUC_{0-4} (i.e., C_0, C_{75min}, and C_4), or AUC_{0-2} (i.e.,C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min}) and incidence of adverse events (leucopenia, infections, diarrhea, anemia, or thrombocytopenia)

Table 24. Studies showing no relationship between adverse events and method of MPA monitoring. Limited sampling strategies – Other (continued)

Study	Population	Treatment	Major Findings/ Comments
Weber[17] 2001 Study design: Case series Length of followup: 6 months	Organ transplanted: Kidney (Renal) Age: Range 2.2-17.8y	Dose: 600 mg/m^2 BID up to 2 g/day maximum Concomitant medications: Cyclosporine A Methylprednisolone	There was no significant association between C_{max}, AUC_{0-4} (i.e., C_0, C_{75min}, and C_4), or AUC_{0-2} (i.e., C_0, C_{20min}, C_{40min}, C_{75min}, and C_{120min}) and incidence of adverse events (leucopenia, infections, diarrhea, vomiting, or abdominal pain).[Note that free MPA C_{max} and free MPA AUC_{0-12} were able to discriminate between patients with or without infections and/or leukemia]

Table 25. Influence of age on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Borrows[69] 2005	Kidney (Renal)	117	Mean: 46 +/- 9y Range: 37-55y	58.1	White 55.6% Indo-Asian 23.1% Afro-Carib 17.9% Other 3.4%	Tacrolimus Methylprednisolone Prednisone	Infective diarrhea, patient survival, graft survival, biopsy proven acute rejection	No association between age and MPA predose concentrations
Bunchman[23] 2001	Kidney (Renal)	100	Inclusion requirement 3 months - 18 years	68	64 patients were from North America, 4 from Australia and 32 from Europe	600 mg/m^2 BID up to 1 g BID	Presumptive rejection, diarrhea, anemia, sepsis, leukopenia, renal function (creatinine clearances) % rejections and adverse events by age group and AUC and Cmax Age groups: <6y 6 to 12y 12 to 18y < 2y	No associations were observed between low MPA and MPAG plasma concentrations and the incidence of acute rejection or of adverse events
Cattaneo[18] 2001	Kidney (Renal)	46	Range 19-61y	63	NR	2 g/day	Creatinine clearance, renal function, rejection episodes, serum creatinine concentration, creatinine clearance	Patients with MPA AUC_{0-12} > 40 µg/mL.h group slightly but significantly younger than patients in the < 40 µg/mL.h group
Dipchand[55] 2001	Heart (Cardiac)	44	Range 29 d-23.5y Median 6.3y	61	NR	various: 15-159 mg/kg	Rejection	Increased MPA predose concentrations were significantly associated with older children

Abbreviations: AUC=Area-under-the-concentration-time curve, BID=Twice daily, C_{max}=Maximum Serum or Plasma Concentration, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, MMF=Mycophenolate Mofetil, NR=Not Reported, PK=Pharmacokinetic, y=Years

Table 25. Influence of age on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Wang [122] 2007	Kidney (Renal)	48	Elderly group: 65.6 +/- 3.6y Adult group: 39.6 +/- 14.3y	67	Chinese	Cyclosporine MMF Prednisone	Acute rejection Severe adverse events: Pneumonia, leukopenia, death	MPA AUC was significantly lower in the elderly group compared to the younger adult group, while there was no significant difference in predose, peak concentrations, or peak times. AUC in the subgroup of elderly patients with severe adverse events was significantly higher than that of elderly patients without severe adverse events.
Weber[17] 2001	Kidney (Renal)	24	Range: 2.2 - 17.8y	61.1	All patients were white	Cyclosporine Methylprednisolone	Acute rejection, adverse events (leucopenia, infections)	In the first week post-transplant, but not at later PK sampling periods, low MPA AUC_{0-12} values were associated with young age MPA AUC_{0-12} and predose MPA concentrations were significantly associated with the risk of acute rejection
Weber, L[112] 1998	Kidney (Renal)	28	Children Mean 10.7 +/ - 0.72y Range 5.9 - 15.3y Adults Mean 45.9 +/- 4.1y Range 20.1 - 59.2y	64	NR	Children: 600 mg/m^2 body surface area BID Adults: 1 g BID	Transplant dysfunction all subjects	Mean MPA AUC_{0-12} in pediatric patients one week post-transplant was 40% higher than in adults, but comparable at three weeks. The AUC_{0-12} values of free MPA at one and three weeks did not differ between children and adults. Children displayed concentration-time profiles of total and free MPA after oral administration of 600 mg/m^2 body surface area twice daily that, in general, were comparable to the profiles of adults receiving 1,000 mg MMF twice daily

Table 26. Influence of gender on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Borrows[69] 2005	Kidney (Renal)	117	Mean: 46 +/- 9y Range: 37-55y	58.1	White 55.6% Indo-Asian 23.1 Afro-Carib 17.9% Other 3.4%	Tacrolimus Methylprednisolone Prednisone	Infective diarrhea, patient survival, graft survival, biopsy proven acute rejection	Multivariable analysis showed that female gender was associated with higher predose concentrations compared to males (effect size: 1.22; 95% CI: 1.12 to 1.31; p = 0.002)
Kuypers[52] 2003	Kidney (Renal)	100	Meidan: 51.5y	59	NR	Daclizumab (31 patients) Tacrolimus Methylprednisolone	Delayed graft function, mild hepatic dysfunction (abnormal liver function)	MPA PK parameters were not influenced by recipient gender
Lu[29] 2005	Kidney (Renal)	29	Mean: 40.0 +/- 12.0y	58.6	NR	Cyclosporine Prednisone Tacrolimus	Rejection	MPA AUC for females was higher than that of males by 34.3% at the same dose of MMF (p=0.0006)

Abbreviatons: AUC=Area-under-the-concentration-time curve, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, NR=Not Reported, PK=Pharmacokinetic, y=Years

Table 27. Influence of ethnicity on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Borrows [69] 2005	Kidney (Renal)	117	Mean : 46 +/- 9y Range: 37-55y	58.1	White 55.6% Indo-Asian 23.1 Afro-Carib 17.9% Other 3.4%	Tacrolimus Methylprednisolone Prednisone	Infective diarrhea, patient survival, graft survival, biopsy proven acute rejection	No association between ethnicity (White, Indo-Asian, Afro-Caribbean, other) and MPA predose concentrations
Shaw[20] 2000	Kidney (Renal)	33	Range: 47+/-9.7y	70	African American: 13 Caucasian: 20	Neoral Steriods	Impaired Renal Function	No significant differences in MPA AUC values or predose concentrations over the 3-month study period in African Americans compared to Caucasians

Abbreviations: AUC=Area-under-the-concentration-time curve, MPA=Mycophenolic Acid, y=Years

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Atcheson[13] 2004	Kidney (Renal)	42	Mean: 44.3 +/- 13.1y	57	Caucasian 98%	Cyclosporine n=32 Tacrolimus n=10 Simulect Diltiazem Prednisolone	Rejection, gastrointestinal events, anemia, hematological events thrombocytopenia and leukopenia), infectious events	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations compared to patients receiving concomitant cyclosporine
Borrows[69] 2005	Kidney (Renal)	117	Mean: 46 +/- 9y Range: 37-55y	58.1	White 55.6% Indo-Asian 23.1% Afro-Carib 17.9% Other 3.4%	Tacrolimus Methylprednisolone Prednisone	Infective diarrhea, patient survival, graft survival, biopsy proven acute rejection	A significant positive association was seen between tacrolimus predose concentration and MPA concentration. There was a significant interaction between this association and time, with larger effect seen early post transplantation
Cantin[58] 2002	Heart (Cardiac)	26	Mean: 54.4 +/- 14y Range: 22–72y	73	NR	Cyclosporine Tacrolimus Corticosteroids	Overall rejection	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations compared to patients receiving concomitant cyclosporine

Abbreviations: AE=Adverse events, AUC=Area-under-the-concentration-time curve, CMV=Cytomegalovirus, CNI=Calcineurin Inhibitors, CsA=Cyclosporin A, CyA=Cyclosporine, GI=Gastrointestinal, MPA=Mycophenolic Acid, NR=Not Reported, PSL-Prednisolone, TAC=Tacrolimus, y=Years

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Heller[77] 2007	Kidney (Renal)	290	Mean: 52.5 +/- 13.4y	62	White 89.8% Black 1.9% Asian 3.2% Other 5.2%	Cyclosporine n=110 Tacrolimus n=180	Diarrhea	Tacrolimus/MMF regimen was associated with a higher incidence of diarrhea compared to Cyclosporine/MMF, although MMF dose was similar in the two groups. MPA AUC was lower in the cyclosporine group, but plasma AcMPAG and MPAG were substantially higher with concomitant cyclosporine compared with tacrolimus.
Hesse[45] 2001	Heart (Cardiac)	20	NR	NR	NR	Tacrolimus Prednisone CsA	Acute rejection (biopsy score comparison)	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations compared to patients receiving concomitant cyclosporine

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Kuypers[36] 2004	Kidney (Renal)	100	Median 51.5y	59	NR	Tacrolimus Methylprednisolone Daclizumab	Acute rejection	There was no significant correlation between tacrolimus dose, $AUC_{0-12,}$ $C_{0,}$ C_{max} , and systolic, diastolic, and mean arterial pressures at any time point after transplantation. Neither for tacrolimus nor for MPA was there a statistically significant difference between recipients with acute rejection and those who remained rejection-free with regard to day 7 AUC_{0-12} , MPA, C_0, C_{max}, or dose. In patients who had an acute rejection, the maximum tacrolimus concentration (t_{max}) was reached significantly faster than in recipients without rejection.
Lu[29] 2005	Kidney (Renal)	29	Mean: 40.0 +/- 12.0y	58.6	NR	Cyclosporine Prednisone Tacrolimus	Acute rejection	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations and MPA AUC compared to patients receiving concomitant cyclosporine

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Mandla[38] 2006	Kidney (Renal)	78 CsA: 68 Tac: 10	Mean: 54y Range: 19-77y	73.1	NR	Tacrolimus Methylprednisolone Prednisone Cyclosporine	Acute rejection,hypoalbuminemia, delayed graft function	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations compared to patients receiving concomitant cyclosporine
Mourad[33] 2001	Kidney (Renal)	51	Range: 32-68y Median: 49y	57	NR	Tacrolimus Corticosteroids	Side effects	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations and MPA AUC compared to patients receiving concomitant cyclosporine
Naito[108] 2006	Kidney (Renal)	25 9 in TAC 3 in CNI, 13 in CsA	Range: 14-60y	64	NR	Cyclosporine Tacrolimus	Creatinine	No significant difference in MPA predose concentrations between tacrolimus versus cyclosporine treated groups No difference in CNI-treated patients compared with patients not receiving concomitant CNIs

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Okamoto[49] 2005	Kidney (Renal)	67	Mean: 38+/-14y	57	NR	Cyclosporine n=35 Tacrolimus n=32	Acute rejection, adverse events (CMV, Varicella, GI disorder) within 2 weeks after transplantation Results for Tac treated group vs CsA treated group	MPA AUC $_{0\text{-}9}$ and predose concentrations in the cyclosporine group were not different in the AE positive group compared with AE negative group. MPA AUC $_{0\text{-}9}$ and predose concentrations in the tacrolimus group were higher in the AE positive group compared with AE negative group within 2 weeks after transplantation
Pawinski[64] 2006	Kidney (Renal)	33	Range: 17–62y Mean: 48y	52.9	NR	Cyclosporine Tacrolimus Prednisone	acute rejection, leucocyte cell count, hemotocrit values, serum creatinine	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations and MPA AUC compared to patients receiving concomitant cyclosporine
Ringe[107] 2001	Liver	30	51.9 (15-66)y	70	NR	Tacrolimus	Acute rejection Diarrhea	Significant correlation between acute rejection and subtherapeutic TAC trough levels, presumably aggravated by poor intestinal drug absorption caused by diarrhea and MMF
Sugioka[76] 2006	Kidney (Renal)	83 Group 1: 63 Group 2: 20	Range: MPA group: 7-69y, PSL group: 11–66y	MPA group: 65.1 PSL group: 55 both: 62.7	NR	Cyclosporine Tacrolimus Prednisone	Leukopenia, Diarrhea	Patients receiving concomitant tacrolimus had significantly higher MPA predose concentrations and MPA AUC compared to patients receiving concomitant cyclosporine

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Tredger[40] 2004	Liver	147 adults 63 children	Median adults: 50.1y children: 3.5y Range adults: 6.9-71.8y Range children: 0.3-19.5y	adults: 53.1 children: 49.2	NR	Cyclosporine Tacrolimus	Acute rejection, all gastrointestinal side effects, low total white cell count, leucopenia, neurological episodes, all infections (bacterial, fungal and viral), other adverse events	Median MPA concentrations were lower with tacrolimus than with either cyclosporine or no CNI comedication
Tsaroucha[24] 2000	Kidney (Renal) Liver Small bowel	Liver: 83 Small bowel: 15 Kidney: 25	Mean: liver: 41.36 +/- 4.56y; small bowel: 18.69 +/- 3.88y; kidney: 44.25 +/- 2.70y	Liver: 70; Small bowel: 40; Kidney: 52	NR	Tacrolimus Steroids	Rejection, graft survival, patient survival	There was no significant difference between any of the patient groups with respect to MPAG concentrations and tacrolimus blood concentrations.
Weber[63] 2006	Kidney (Renal)	79 condition 1: 54 condition 2: 25	Range: German study: 3.17-16.0y, suspension trial: 1.0-16.0y	German study: 61.1, suspension trial: 68.0, both: 63.3	NR	German study: Cyclosporine Methylprednisolone Corticosteroids Suspension trial: Cyclosporine Prednisone	Acute rejection, side effects such as leukopenia and infections	Association between the risk of acute rejection episodes and MPA AUC $_{0\text{-}12}$ values in pediatric renal transplant recipients on an immunosuppressive triple drug therapy with MMF, CsA and corticosterioids.

Table 28. Influence of the concomitant use of calcineurin inhibitors on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Zakliczynski [70] 2005	Heart (Cardiac)	76	Mean: 41.9 +/- 16y	72	NR	Cyclosporine Tacrolimus Prednisone Azathioprine	Gastrointestinal tract irritation (diarrhea, nausea, vomiting, epigastric pain), leukopoenia, anemia	A significant positive correlation between MPA and CyA concentration was noted in the group of patients with impaired liver function but there was no correlation between MPA and TAC concentration in this group. No correlation was noted between CyA and MPA concentration, and TAC and MPA concentrations, in the group of patients without impaired liver function. The incidence of supratherapeutic MPA concentrations was significantly higher in patients receiving TAC.

Table 29. Influence of the concomitant use of other medications on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Borrows [69] 2005	Kidney (Renal)	117	Mean: 46 +/- 9y Range: 37-55y	58.1	White 55.6% Indo-Asian 23.1 Afro-Carib 17.9% Other 3.4%	Tacrolimus Methylprednisolone Prednisone	Infective diarrhea, patient survival, graft survival, biopsy proven acute rejection	Treatment with oral augmentin, ciprofloxacin, or metronidazole was associated with a reduction in MPA predose concentrations. Treatment with intravenous antibiotics (vancomycin, tazocin, and carbopenems) showed no effect. No association between MPA predose concentrations and the use of oral prednisolone, ferrous sulfate, calcium carbonate, or ganciclovir.
Kreis[50] 2000	Kidney (Renal)	78 Condition 1: SIR: 40 Condition 2: CsA: 38	SIR: 43.5 +/- 10.9y (22-62); CsA: 42.9 +/- 11.4y (18-60)	SIR: 70 CsA: 71	NR	Cyclosporine Corticosteroids Sirolimus	Acute rejection rate at 12 months, graft survival, patient survival, renal function Compares Sirolimus group to Cyclosporin group	Average daily doses of MMF were significantly lower in the sirolimus group. MPA predose concentrations were significantly higher in the sirolimus group.

Abbreviations: AUC=Area-under-the–concentration-time curve, CMV=Cytomegalovirus, CNI=Calcineurin Inhibitors, CsA=Cyclosporin A, GI=Gastrointestinal, MMF=Mycophenolate Mofetil, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, NR=Not Reported, PK=Pharmacokinetic, PSL=Prednisolone, SIR=Sirolimus, TAC=Tacrolimus, y=Years

Table 29. Influence of the concomitant use of other medications on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant (continued)

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Merkel[22] 2005	Kidney (Renal)	35	Mean: 44 +/- 13.6y Range: 13–63y	68.6	NR	Cyclosporine Corticosteroids Prednisone	Kidney function (concentration of serum creatinine), rejection, adverse effect (CMV infection)	No effect of concomitant steroids or furosemide on MPA or MPAG predose concentrations. Positive correlation between xipamide (a thiazide diuretic) and MPA predose concentrations. A negative correlation between diltiazem and MPA predose concentrations.
Mudge [65] 2004	Kidney (Renal)	45	Mean: 45.2 +/- 13.2y	55	White 98%	Cyclosporine Tacrolimus Prednisone	Toxicity (GI, hematologic, infectious adverse events), biopsy-proven acute rejection (defined according to Banff 1997 criteria)	No significant effect of oral iron supplements on MMF absorption, MMF toxicity, rejection rates, or frequencies of anemia, leucopenia, thrombocytopenia, infection or gastrointestinal intolerance as measured by MPA AUC
Wolfe[78] 1995	Kidney (Renal)	12	Mean: 36 +/- 13y Range: 20 to 57y	100	NR	Cyclosporine Prednisone Ganciclovir in 2 arms, one arm alone and 1 arm combined with MMF Azathioprine	potential drug interaction between MPA and ganciclovir, creatinine clearance	PK parameters of MPA and MPAG were unchanged by the addition of ganciclovir

Table 30. Influence of comorbidity on the utility of monitoring mycophenolic acid in patients who receive a solid organ transplant

Study	Organ	n	Age	% Male	Race	Medications	Health Outcomes Reported	Results
Behrend[25] 1997	Kidney (Renal)	57	NR	NR	NR	Cyclosporine Corticosteroids	graft function dialysis adverse events infections	No effect of graft function or dialysis on MPA concentrations. Increase of MPAG with decreasing graft function.
Brunet[66] 2006	Liver	15	Range: 29 – 66y	60	NR	Tacrolimus Methylprednisolone Daclizumab	Acute rejection	No significant correlation between liver function and MPA concentration and AUC.
Cattaneo[18] 2001	Kidney (Renal)	46	Range 19-61y	63	NR	Cyclosporine Prednisone CSA Neoral	Creatinine Anemia Diarrhea Infections	MPA predose concentrations and MPA AUC_{0-12} were positively and significantly correlated with patients' creatinine clearance values.
Johnson[123] 1998	Kidney (Renal)	31	Mean for groups 1-5 44.5 +/- 15.9y, 41.7 +/- 10.3y, 43.8 +/- 10.8y, 45.3 +/- 15.0y, 45.3 +/- 8.5y	Mean for Groups 1-5 83.3, 66.6, 100, 57.1, 66.6	6 whites in group 1 & 2, 3 white and 3 black in group 3, 6 white and 1 native American in group 4, 3 white 1 black and 2 native Americans in group 5	None	GFR	MPA clearance was not associated with changes in GFR. C_{max} increased as GFR decreased. MPAG clearance correlated with GFR (r^2 =0.90) Clearance of MPA and MPAG were unaffected by hemodialysis, with losses during hemodialysis representing less than 10% of the dose administered

Abbreviations: AUC=Area-under-the-concentration-time curve, C_{max}=Maximum Serum or Plasma Concentration, GFR=Glomerular Filtration Rate, MPA=Mycophenolic Acid, MPAG=Mycophenolic Acid Glucuronide, NR=Not Reported, y=Years

Chapter 4. Discussion

Discussion of the Evidence for the Key Questions

Question 1. What is the Evidence That Monitoring Mycophenolic Acid in Patients who Receive a Solid Organ Transplant Results in a Lower Incidence of Transplant Rejections and Adverse events Compared to Patients who are not Monitored?

Only three studies addressed this question. The first, by Meiser et al.,[7,8] was really two case series reported together. The study was not designed to compare monitoring versus no monitoring, so the authors did not report important comparative data. For example, there was no presentation of mean plasma predose concentrations for concentration controlled patients who did not have rejection, nor was there a statistical comparison of intra- or inter-group differences. Therefore, one cannot conclude from this study that outcomes or adverse events were affected by monitoring versus no monitoring. The second study, by Flechner et al.,[9] found no evidence to suggest that monitoring is associated with a lower incidence of rejection. In contrast, there was evidence to suggest that monitored patients could have a lower incidence of certain gastrointestinal adverse events. However, the evidence regarding rejection and gastrointestinal problems could have been confounded by starting dose. The initial dose of MMF (Mycophenolate Mofetil) was different (2 g in the fixed dose group and 1 g in the monitored group), so any potential effect of a higher starting dose in the monitored group could have been obscured as a result of the study design. As well, more gastrointestinal adverse events might have occurred in the fixed dose group regardless of monitoring because there is evidence of a positive association between larger MMF doses and adverse events.[12]
The third study,[10] the first published randomized controlled trial (RCT) to compare monitoring versus no monitoring of mycophenolic acid (MPA) in any patient group, found a lower incidence of treatment failures (driven primary by a lower incidence of acute rejections) in the monitored (concentration-controlled) group. Although the RCT suggests a potential benefit for monitoring, it is limited to adult kidney transplant patients, so the efficacy of monitoring in other patient populations is still unknown. Likewise, the clinical applicability of the trial's limited area under the curve (AUC) sampling strategy, or the applicability of the 40 mg·h/L MPA target dose, to these other populations is also unknown.

Two further RCTs comparing concentration-controlled versus fixed dose patients have, at the time of this report, been completed yet not published. Some of the data from these trials are publicly available in abstract form. The first RCT is the Opticept study from the United States (Roche protocol number ML 17225).[124-126] This is a 2 year, open label RCT in kidney transplant patients designed to evaluate fixed dose MMF (1 g BID) versus concentration-controlled MMF (predose-based dose adjustments of 1.3 μg/mL or more in cyclosporine treated patients and 1.9 μg/mL in tacrolimus treated patients). The primary outcome is renal function measured as mean percent change in calculated GFR (Glomerular filtration rate). So far, the investigators have reported that baseline characteristics and renal function were similar between groups in a total

sample of 522 persons. Personal correspondence with one of the study investigators (Roy Bloom) and Roche indicate that no results have been published in peer reviewed journals. As well, no timelines were available with respect to when further details of the study might be published.

The Fixed Dose Concentration Controlled (FDCC) RCT[127-129] is a multicenter RCT conducted in Europe, Canada, South America, Asia, and Australia. Kidney transplant patients (n=901) were randomized to fixed dose MMF (2 g daily for adults, 1.2 g daily per square meter for children) or concentration controlled MMF based on a target MPA AUC_{0-12} range of 30 to 60 h.mg/L. The primary outcome was a composite of patients who suffered any of the following: biopsy proven acute rejection, graft loss, death, or discontinuation of MMF therapy. According to personal correspondence with lead author Teun van Gelder, the main results have been submitted to the Lancet. The results from a substudy of the FDCC trial have been published.[77] In the substudy, which reports on 290 patients, 147 received the fixed dose and 143 received the concentration controlled dose. The purpose of the substudy was to examine the incidence of diarrhea. The patients were further divided by type of concomitant therapy: cyclosporine and MMF (n=56 fixed dose; n=54 concentration-controlled) or tacrolimus and MMF (n=91 fixed dose; n=89 concentration controlled). Within the cyclosporine/MMF group and the tacrolimus/MMF group, there was no difference in the number of cases of diarrhea between fixed or concentration controlled patients ($p>0.05$). When the groups were compared to one another, the incidence of diarrhea was higher in the tacrolimus/MMF group (n=69 versus n=17 in the cyclosporine/MMF group [$p<0.001$]). MPA AUC_{0-12} values did not differ between patients who suffered diarrhea and patients who did not ($p>0.05$).

While the results of these other two multicenter studies are being anxiously awaited, it should be noted that the study populations involve kidney transplant recipients, so the results may not be directly applicable to other solid organ transplant subpopulations. Certainly, RCTs in these other subpopulations are warranted before the key question can be more fully answered.

Question 2. Does the Incidence Differ by any of the Following?

2a: MPA Dose and Dose Frequency

Overall, the evidence to support an association between MMF dosage and rejection is outweighed by the evidence against. However, an equal number of studies supported and refuted the association between MMF dosage and adverse events. Unfortunately, most of the evidence was in the form of case series. Furthermore, even the relatively few higher quality studies (e.g., cohort studies) were not designed to address whether MMF dosage is associated with rejection or adverse events. These factors, coupled with the diversity of other variables in the studies (e.g., concomitant medications, different lengths of followup, specific adverse events evaluated) make it difficult to provide a clear answer to the question. What is direly needed are RCTs that compare patients who are monitored to patients who are not monitored. Ideally, these trials would permit comparisons at different fixed doses and at different targets for concentration control.

2b: Type of MPA (mycophenolate mofetil [CellCept®], enteric-coated mycophenolate sodium [Myfortic®])

The recently introduced, enteric-coated, delayed release formulation of MPA (i.e., enteric-coated mycophenolate sodium (ECMPS)) was designed to reduce upper gastrointestinal adverse events. ECMPS delivers the same MPA exposure (AUC) as MMF and is therapeutically equivalent, but leads to higher C_0 concentrations.[130] None of the included studies directly compared ECMPS with MMF. Studies that were not helpful in answering question 2b included those without control group, e.g. with all patients switched from MMF to mycophenolate sodium. Due to small numbers, adverse events or rejection events were not observed or could not be correlated with PK parameters in many studies, so question 2b could not be answered.

Clinicians should be aware of the potential for higher predose plasma or serum concentrations (C_0) with ECMPS compared to MMF. Full AUCs are not expected to be different between the two formulations, but are too difficult to use in standard practice situations. Predose concentrations or abbreviated sampling strategies are more realistic, but due to the delayed absorption of ECMPS, they will have to be validated separately from MMF. Future randomized concentration-controlled trials comparing no monitoring to monitoring with different target PK parameters could establish therapeutic concentrations for mycophenolate sodium and evaluate the utility of monitoring at the same time.

Question 3a: Does the Incidence Differ by Total Versus Free MPA, Albumin, Metabolites, Genetic Differences or by Analytical Method of MPA Monitoring?

Does the Incidence Differ by Total Versus Free MPA or Albumin?

Only free, protein unbound drug molecules are available for receptor binding. Therefore, measurements of free MPA (fMPA) may theoretically be expected to correlate better with outcomes than total MPA. However, none of the included studies confirmed this hypothesis, although free (not total) MPA was found to be associated with infections and haematological adverse events.[13,14,17] Thus, there is potential for the utility of fMPA monitoring, but this has yet to be demonstrated in an RCT. Many of the studies in this report showed that impaired renal function and hypoalbuminemia coincide with elevated mycophenolic acid glucuronide (MPAG) and fMPA, but not total MPA. The mechanisms involved are complex. In renal failure, MPAG excretion is decreased, the accumulated metabolite displaces MPA from albumin, and the added fMPA is available not only for therapeutic or toxic effects, but also for hepatic clearance. Measures of total MPA do not reflect these processes and might even be decreased. Given the added complexity and limited availability of fMPA testing, an alternative would be to measure total MPA while taking renal function and serum albumin into account. Recently, however, Roche has introduced an Inosine 5'-monophosphate dehydrogenase (IMPDH) based assay for free and total MPA. A CEDIA assay is now available from Microgenics.

Does the Incidence Differ by Genetic Differences or Metabolite Concentrations?

The pharmacogenetic study by Naesens et al.[79] showed that carriers of the two MRP2 (multidrug resistance protein) SNPs (single nucleotide polymorphisms) were protected from reduced MPA exposure in mild liver dysfunction. The other genetic study, by Satoh et al.,[30] found associations between MPA and genes, genes and diarrhea, and MPA and rejection. The clinical relevance of both studies is unclear, as they do not suggest how monitoring of MPA could be augmented to prevent rejection or adverse events. The biochemical mechanisms are not well enough understood and genetic screening for the mentioned polymorphisms does not seem warranted. More basic and clinical research appears necessary.

The studies regarding metabolites yielded few positive results. The fat malabsorption results,[16] based on five patients, apply to a very specialised population. The only other significant associations were those between AcMPAG (acyl glucuronide metabolite of mycophenolic acid), MPAG, and anemia, but not to other adverse events or efficacy endpoints.[15] Monitoring of metabolites cannot be generally recommended based on these results. The pharmacokinetics of MPA is very complex, involving enterohepatic recirculation, competition of parent drug and MPAG for albumin binding, many drug-drug interactions and other complicating factors. Although the active metabolite (AcMPAG) may hold some promise in predicting toxicities, the mechanisms leading to adverse events, especially GI effects, are not yet understood and should be studied in the laboratory. Larger, randomized trials are necessary to establish the utility of monitoring MPA and its metabolites.

Does the Incidence Differ by Assay Method?

In two studies,[26,27] HPLC (high-performance liquid chromatography) and EMIT (enzyme-multiplied immunoassay technique) performed similarly well in the assessment of acute rejection risk in pediatric kidney transplant patients. As expected, EMIT cut off values were higher than those derived from HPLC measurements. This is because immunoassays often show a positive bias compared to more specific chromatographic techniques. As well, the EMIT for MPA cross reacts with AcMPAG, an active metabolite of MPA.[119] Theoretically, EMIT could be advantageous over HPLC because it might reflect total immunosuppressive activity better, although this is not certain because cross reactivities are concentration dependent, and the two studies did not find EMIT to be superior. Potentially higher cut off values for EMIT mean that target ranges for total MPA $AUC_{0\text{-}12}$ or C_0 will have to be derived separately for HPLC and EMIT.

The general implications of the findings are difficult to assess. Only two studies[26,27] directly compared HPLC and EMIT; the study populations in both studies were pediatric patients. It remains to be seen whether diagnostic sensitivities and specificities would differ between methods in other populations. In one study,[27] the age and sex distributions of pediatric patients were not provided, so it was difficult to know exactly to whom the diagnostic sensitivities and specificities were applicable. As well, there is currently no information about the comparative merits of HPLC or EMIT in conjunction with other assay methods, such as HPLC-MS, because no study was undertaken to make such comparisons.

Adverse events were considered in one study[26] and MPA PK (pharmacokinetic) parameters were not found to predict them, regardless of assay method. However, there is some evidence in

this report that PK parameters can distinguish between persons with and without adverse events. Perhaps the findings apply only to the specific profile of pediatric patients enrolled in the study. Another possibility is the potential for bias. Weber et al.[26] did not explain the basis upon which their patients were chosen, thus raising the issue of selection bias. Verification bias may also have been present because some patients did not undergo biopsy, nor was there any reporting of stratification according to the factors that triggered biopsy.

Another issue with the two studies[26,27] that are pertinent to Question 3aii was the lack of clarity concerning how the operating points on the ROC (receiver operator characteristic) curves were chosen. Other choices of decision levels and their corresponding sensitivity/specificity pairs may have been more appropriate, depending on the prior probability of rejection, the importance of correct classification, and the relative undesirability of false positive or false negative errors.

Ultimately, since the goal of monitoring is the prevention (not diagnosis) of rejection and adverse events, the utility of monitoring will have to be assessed in trials designed to study this goal. A factorial trial would be appropriate to study monitoring versus not monitoring in conjunction with the efficacy of measuring MPA using different assay methods, including the new assays for total and free MPA mentioned above. Alternatively, reference therapeutic PK parameters for different assay methods could first be derived from observational studies and then tested in an RCT. A similar strategy may apply for all key questions.

3b: Does the Incidence Differ by Method of MPA Monitoring (Full AUC or Limited Sampling Strategies [i.e., Predose Concentrations, 2 hour Post Dose Concentrations, Other])?

Overall, the evidence to support an association between full AUC (AUC_{0-12}) and rejection outweighs the evidence against. The opposite is true for the association between full AUC and adverse events. There are more studies showing that predose (C_0, C_{min}, or C_{12}) compared to full AUC measurements are associated with both rejection and adverse events, but there are an even greater number of studies demonstrating that trough has no association. Equal numbers of studies demonstrate positive versus no associations between monitoring using other limited sampling strategies and rejection, but when adverse events are considered there are more studies showing a lack of association rather than an association.

Since full AUC measurements are cumbersome and impractical to use clinically, and more studies demonstrate the lack of utility of trough in discriminating between patients with and without rejection or adverse events, we are left to consider other limited sampling strategies. To date, C_2 has not been well studied and there appears to be no consensus regarding the utility of other limited sampling strategies in discriminating between rejectors and non rejectors. However, there are three times as many studies that demonstrate the lack of utility of other limited sampling strategies in predicting adverse events.

The evidence for answering this question is limited by the objectives of the included studies. Most of the studies were observational or case series designs developed with the intention of studying the biological or pharmacological effects of MMF dosing or MMF in combination with a calcineurin inhibitor. Some earlier exploratory studies were undertaken to obtain information on the associations between PK parameters and dosing, time, or other PK parameters. None of the studies were designed to compare the incidence of rejection or adverse events in groups of patients whose MMF doses were controlled using different sampling strategies. Although many

studies had multiple sampling strategies measured on the same patients, these measurements were not used for dose adjustment. Rather, the authors of these studies sought to examine whether mean measurement values were associated with an outcome such as rejection or adverse events. These data are hypothesis generating because they can provide insight into the types of sampling strategies to use in monitoring, but they do not actually indicate whether monitoring and dose adjustment would have an affect on outcomes.

Question 3b can best be answered with head-to-head (RCT) comparisons of monitoring and dose adjustment using different sampling strategies. To date, there is only one published study comparing concentration-controlled and fixed dose MMF.[10] In the concentration-controlled group, the investigators used a 3-sample limited sampling strategy (developed by Bayesian techniques) to predict MPA AUC. Although the concentration-controlled group had significantly lower treatment failures and acute rejections, there was no significant difference in incidence of most adverse events, save for the incidence of herpes infections, which was greater in the concentration-controlled group. As eloquently articulated in an editorial accompanying the published trial, "One is left to wonder that despite an elegant and elaborate algorithm for dose changes, could these same [adverse effect] results have been obtained by simply administering higher doses of MMF without MPA monitoring?"[131]

Question 4. Does the Evidence for Monitoring MPA Differ by any of the Following – Age, Gender, Ethnicity, Concomitant use of Calcineurin Inhibitors, Concomitant use of Other Medications, Comorbidity?

Across all parts of Question 4, most of the evidence from the literature search did not directly address the key question. Studies of direct relevance would have evaluated whether monitoring MPA in recipients of solid organ transplants would have led to a lower incidence of rejections or adverse events compared to not monitoring, with subanalyses (specified a priori) stratified by factors such as age, gender, ethnicity, concomitant use of medications, and comorbidities. To date, no such study exists.

The majority of included studies focused on adults and kidney transplant recipients. Few studies involved children, the elderly, or other solid organ transplants. Study findings were difficult to compare because measures of MPA in plasma or serum sometimes exhibit large intra- and inter-patient variability over time post transplant. Moreover, the factors of concern (e.g., age) in this question were not consistently addressed in all of the included studies. Inconsistency was also a hallmark of outcome definition or selection, thereby further detracting from comparability. For example, rejection was inconsistently defined, sometimes clinically via Banff criteria and sometimes using surrogate endpoints such as GFR or serum creatinine. A consistent basket of adverse events was also not the norm. Many studies looked at particular adverse events (e.g., gastrointestinal, liver dysfunction) or did not clearly define the types of adverse events that were under examination. Some published studies, primarily rapid communications such as the work of Behrend et al.,[25] provided limited raw data to support descriptive results and conclusions.

Based on the evidence that could be gleaned from the included studies, certain patient demographics appeared to influence MPA PK parameters. Within pediatric populations, the evidence suggested that younger children may require a higher MMF dose to achieve a specified MPA concentration. Similarly, the evidence suggests that the elderly have lower MPA exposure

compared to younger adults receiving the same dose of MMF. However, the bulk of the evidence indicated no association between patient age and MPA PK parameters in general (i.e., over all age ranges without stratification into pediatric and adult populations). Regarding gender, the evidence suggested AUC_{0-12} and predose concentrations might be higher in women, but the impact of these findings for monitoring rejection or adverse events was not studied. Race and ethnicity did not appear to influence PK parameters.

Calcineurin inhibitors are co-administered frequently with MMF and many studies examined the relationship between these drugs and MPA PK parameters. The evidence found that exposure to MPA is higher in patients receiving tacrolimus compared to cyclosporine, with lower doses of MMF required in combination with tacrolimus to achieve adequate MPA exposure. This difference is explained by the inhibition of the enterohepatic circulation of MPA by cyclosporine. Concomitant use of medications not only influences the MPA exposure but also may affect the utility of therapeutic drug monitoring (TDM). If a solid organ transplant recipient is receiving four different immunosuppressants with a low rejection risk, the overall immunosuppressant effects depend to a much lesser degree on the correct dosing of MPA, whereas in a regimen with only two immunosuppressants and a higher risk of rejection, the overall adequacy of immunosuppression depends heavily on the correct dosing and exposure of MPA.

The effect of renal function on MPA PK parameters was addressed in a number of studies, but the findings were inconsistent and inconclusive.

Question 5. What is the Short- and Long-Term Cost-Effectiveness of Avoiding Acute Rejection due to MPA Monitoring?

The published literature contains no data on the cost effectiveness of monitoring versus no monitoring in solid organ transplants. Therefore, it is not possible to answer this key question.

At the time this report is being written, the authors of the lone published RCT on monitoring versus no monitoring[10] report that an economic evaluation of their trial results is ongoing. These results, once published, will be an important addition to the literature. For a monitoring strategy to be cost-effective, the additional costs of implementing the monitoring protocol would have to be exceeded by the savings associated with treating fewer rejections or adverse events. From the perspective of a public or private health insurer that is considering whether to reimburse the cost of monitoring, it is not sufficient to simply look at cost data. Effectiveness data (e.g., quality adjusted life years [QALYs]) should also be considered and evaluated using standard methods of cost effectiveness analysis.[100] The result of such an analysis would be to obtain an incremental cost per unit of effect (e.g., cost per QALY). This ratio can be used to compare monitoring with other competing healthcare programs, thereby allowing insurers to determine which program is most effective per unit of cost. Such information can be used to help make decisions about which program(s) to reimburse.

Limitations of This Evidence Report

Only English language, published studies were included in the report. The available budget and timelines limited the McMaster University Evidence-based Practice Center's (MU-EPC's) ability to obtain, translate, and abstract non English or unpublished studies. In addition, study authors were not contacted to obtain supplemental data that were not presented in the published

articles. It has been the MU-EPC's experience that the majority of authors do not respond in a timely fashion, if at all, to requests for information. These omissions may have introduced publication bias into this evidence report.

Virually all of the studies involve MMF, not ECMPS. The generalizability of MMF data to ECMPS should be handled with extreme caution because differences in absorption kinetics make, it difficult to substitute algorithms developed for limited sampling strategies in MMF to ECMPS. In addition, the utility of predose concentration measurements may be even more limited for persons receiving ECMPS than for persons receiving MMF because the enteric-coated formulation is particularly prone to delays in gastric emptying time. As a result, very high morning predose concentrations can be encountered.

The evidence report contains all of the relevant literature to address the key questions up to and including October 2007. This means that new and potentially important studies published after this date will not be included unless a future update of the report is commissioned.

Conclusions

The state of knowledge about therapeutic drug monitoring of MPA in solid organ transplants is still in its infancy. This is especially so for organs other than the kidney because the overwhelming majority of published studies involve kidney transplant patients. There is direct evidence from only one study[10] to suggest that monitoring would reduce the incidence of rejection in adult kidney transplant patients. Two soon to be published trials (Opticept, FDCC) will supplement this limited evidence, but many issues will remain outstanding. These issues include the optimal method of MPA monitoring. The most complete and most studied method is the full AUC ($AUC_{0\text{-}12}$), but this procedure requires at least eight blood samples over a 12 hour dose interval and is therefore impractical to use in most clinical settings. Evidence for the utility of limited sampling strategies (e.g., predose [C_0, C_{min}, C_{12}]) is equivocal at best and largely based on case series or observational studies whose primary purpose was something other than to compare strategies. Other limited sampling strategies (e.g., C_2, multiple sample strategies, etc.) have not been studied well enough to assess their utility for monitoring.

Another issue is the lack of an obvious MPA target concentration to govern dose adjustment. The selection of such a concentration depends on the sampling strategy and may be frustrated by the wide intra-patient variability in MPA plasma concentration time profiles, especially if the influence of time after transplantation is not accounted for. Even if a standardized target concentration can be agreed upon, there are too few studies to guide the choice of assay or suggest the best frequency for measuring MPA in the plasma or serum. At this point, there is no evidence to even suggest whether assay type matters.

The utility of monitoring MPA is further muddled by the fact that resolutions to all of the aforementioned issues may differ by type of drug (MMF, ECMPS), dose, population characteristics (adult, pediatric), comorbidity, concomitant medications, and type of organ transplanted. There is certainly evidence to suggest that these items matter (e.g., physicians targeting MPA predose concentrations must note the existence of higher morning C_0 concentrations with ECMPS[130]), but the literature provides no clear guidance on how to operationalize them clinically. Furthermore, there is little data available on the long term pharmacokinetics of MPA. The extent to which changes in pharmacokinetic parameters over time post transplant can affect the utility of TDM needs to be the subject of investigation.

Another knowledge gap is in the area of economic evaluation. No published study has contained an examination of whether monitoring is cost effective versus no monitoring. The results of such an analysis could influence the reimbursement decisions of private or public health insurers. These decisions are important because they affect patient access to treatment.

Quality is also an issue. Reporting of some essential features of RCT design (e.g., method of randomization, blinding) and observational study design (e.g., blinding) was lacking in most studies. Additionally, only 28 of 75 observational studies reported attempts to control confounding. Since none of the observational studies contained direct evidence to address the key questions, the studies can be regarded as hypothesis generating rather than hypothesis confirming. The quality issue further reinforces the notion of hypothesis generation versus confirmation. Studies with quality challenges may not have valid results because of bias and confounding. Consequently, the results of these studies should be verified in future research, preferably using well-designed RCTs.

Overall, the published evidence on MPA monitoring is inconclusive, with some studies suggesting potential benefits and other studies suggesting no benefit. This makes the issuance of clinical recommendations difficult. There is no evidence, except for one published RCT, to suggest that monitoring is more or less beneficial than not monitoring. Until there is more evidence on the utility of routine MPA monitoring in solid organ transplant recipients, patients, clinicians, and other stakeholders (e.g., public and private insurers) will have to decide on a case by case basis whether the possible but uncertain benefits are worth the extra time and expense of monitoring.

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List of Acronyms/Abbreviations

AcMPAG	Acyl Glucuronide Metabolite of Mycophenolic Acid
AHRQ	Agency for Healthcare Research Quality
AMED	Allied and Complementary Medicine
AUC	Area Under the -Curve
CI	Confidence Interval
CNI	Calcineurin Inhibitor
CMV	Cytomegalovirus
C_0	Predose Trough Serum or Plasma Concentration
C_{MAX}	Maximum Serum or Plasma Concentration
ECrCl	Estimated Creatinine Clearance
ECMPS	Enteric-coated Mycophenolate Sodium
EMIT	Enzyme-Multiplied Immunoassay Technique
fMPA	Free Mycophenolic Acid
GFR	Glomerular Filtration Rate
HPLC	High-Performance Liquid Chromatography
HPLC-MS	High-Performance Liquid Chromatography-Mass Spectrometry
HRR	Hazard Rate Ratio
IMPDH	Inosine 5'-Monophosphate Dehydrogenase
LSS	Limited Sampling Strategy
MDR	Multidrug Resistance
MRP	Multidrug Resistance Protein
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
MPAG	Mycophenolic Acid Glucuronide
MU-EPC	McMaster University Evidence-Based Practice Center
OAT	Oroanal Transit Time
OCTT	Orocecal Transit Time
PK	Pharmacokinetic
QUALYs	Quality Adjusted Life Years
RCT	Randomized Controlled Trial
ROC	Receiver Operator Characteristic
RR	Relative Risk
SNP	Single Nucleotide Polymorphisms
SRS	Systematic Review Software
TDM	Therapeutic Drug Monitoring
TEP	Technical Expert Panel
TOO	Task Order Officer
UGT	Uridine Diphosphoglucuronosyltransferase

Appendix A. Exact Search Strings

Database: Ovid MEDLINE®

1. Mycophenolic Acid/
2. mmf.ti,ab.
3. myfortic.mp.
4. cell?ept.mp.
5. mycophenol$.mp.
6. mofetil.mp.
7. mycofenolate.mp.
8. or/1-7
9. exp Kidney Transplantation/
10. exp Heart Transplantation/
11. exp liver transplantation/ or exp pancreas transplantation/
12. exp Lung Transplantation/
13. exp Graft Rejection/
14. exp Organ Transplantation/
15. ((transplant$ or graft) adj4 (kidney or renal or lung$ or cardiac or heart or pancreas or liver or organ or reject$ or patient$)).ti,ab.
16. or/9-15
17. drug monitoring/ or monitoring, immunologic/
18. Dose-Response Relationship, Drug/
19. exp Pharmacokinetics/
20. (monitor$ or sampl$ or measur$).ti,ab.
21. or/17-19,20
22. 16 or 21
23. 22 and 8
24. (transplant immunology or transplant infectious disease or transplant international or transplantation or transplantation bulletin or transplantation proceedings or transplantation reviews or transplantation science).jn.
25. 24 and 8
26. 23 or 25
27. exp *Cell Transplantation/
28. 26 not 27
29. humans/
30. animals/
31. 29 and 30
32. 30 not 31
33. 28 not 32

Database: EMBASE®

1. Mycophenolic Acid/

2. mmf.ti,ab.
3. myfortic.mp.
4. cell?ept.mp.
5. mycophenol$.mp.
6. mofetil.mp.
7. mycofenolate.mp.
8. exp Mycophenolic Acid 2 Morpholinoethyl Ester/
9. or/1-8
10. exp organ transplantation/
11. exp Graft Rejection/
12. Graft Recipient/
13. ((transplant$ or graft) adj4 (kidney or renal or lung$ or cardiac or heart or pancreas or liver or organ or reject$ or patient$)).ti,ab.
14. or/10-13
15. Dose-Response Relationship, Drug/
16. drug monitoring/ or monitoring, immunologic/
17. exp pharmacokinetics/
18. or/15-17
19. 14 or 18
20. 19 and 9
21. (transp sci or transplant immunology or transplant international or transplantation or transplantation proceedings or transplantation reviews).jn.
22. 21 and 9
23. exp *Stem Cell Transplantation/
24. human.sh.
25. nonhuman.sh.
26. animal.sh.
27. animal experiment.sh.
28. 25 or 26 or 27
29. 24 and 28
30. (monitoring or sampling or measur$).ti,ab.
31. 30 and 9
32. 31 or 20
33. 32 or 22
34. 33 not 23
35. 34 not 28
36. 34 and 29
37. 35 or 36

Database: EBM Reviews - Cochrane Central Register of Controlled Trials®

1. Mycophenolic Acid/
2. mmf.ti,ab.
3. myfortic.mp.

4. cell?ept.mp.
5. mycophenol$.mp.
6. mofetil.mp.
7. mycofenolate.mp.
8. or/1-7
9. exp Kidney Transplantation/
10. exp Heart Transplantation/
11. exp liver transplantation/ or exp pancreas transplantation/
12. exp Lung Transplantation/
13. exp Graft Rejection/
14. exp Organ Transplantation/
15. ((transplant$ or graft) adj4 (kidney or renal or lung$ or cardiac or heart or pancreas or liver or organ or reject$ or patient$)).ti,ab.
16. or/9-15
17. drug monitoring/ or monitoring, immunologic/
18. Dose-Response Relationship, Drug/
19. exp Pharmacokinetics/
20. (monitor$ or sampl$ or measur$).ti,ab.
21. or/17-20
22. 16 or 21
23. 22 and 8
24. (transplant immunology or transplant infectious disease or transplant international or transplantation or transplantation bulletin or transplantation proceedings or transplantation reviews or transplantation science).jn.
25. 24 and 8
26. 23 or 25
27. exp *Cell Transplantation/
28. 26 not 27

Database: EBM Reviews - Cochrane Database of Systematic Reviews®

1. mmf.ti,ab.
2. myfortic.mp.
3. cell?ept.mp.
4. mycophenol$.mp.
5. mofetil.mp.
6. mycofenol$.mp.
7. or/1-6 (34)
8. ((transplant$ or graft) adj4 (kidney or renal or lung$ or cardiac or heart or pancreas or liver or organ or reject$ or patient$)).ti,ab.
9. (monitor$ or sampl$ or measur$).ti,ab.
10. 8 or 9
11. 10 and 7

Database: BIOSIS® Previews

1. TS=(mycophenol*)
2. TS=transplant*
3. #2 AND #1
4. TS=(mycophenol* OR myfortic OR cellcept or mofetil)
5. CH=mycophenolate mofetil
6. #5 OR #4
7. MQ=organ transplantation
8. TS=((liver OR kidney OR renal OR pancrea* OR heart OR cardiac OR lung OR organ OR reject* OR patient) SAME (transplan* OR graft))
9. #8 OR #7
10. 10.#9 AND #6

Appendix B. Forms/Guides

Level 1 – Title and Abstract Screening

	YES / MAYBE (continue)	NO (stop)	Is a Case Series (continue)	
1. Is the paper published in English?	☐	☐	☐	Clear
2. Is the publication a peer reviewed full report of an RCT, cohort study, or case-control study (is not a case report, review, overview, discussion piece, conference report/proceeding, abstract, editorial, or letter to the editor)?	☐	☐	☐	Clear
3. Are outcomes reported for human subjects with solid organ transplants?	☐	☐	☐	Clear
4. Does the study involve measurement of any form of MPA in the blood?	☐	☐	☐	Clear

Submit Data

Level 2 – Full Text Screening

	YES (continue)	NO (stop)	
1. Is this report published in English?	☐	☐	Clear
2. Is the publication a peer reviewed full report of an RCT, cohort study, case-series or case-control study (is not a case report, review, overview, discussion piece, conference report/proceeding, abstract, editorial, or letter to the editor)?	☐	☐	Clear
3. Does the study report on humans with solid organ transplants as the subjects?	☐	☐	Clear
4. Is any form of MPA measured in the blood?	☐	☐	Clear
5. Is any form of MPA monitored in the blood (measured with the intent of using the result for any action, based on the MPA blood level)?	☐	☐	Clear
6. Are MPA blood levels associated with any clinical health outcome?	☐	☐	Clear
7. Is there any indication that this paper may be a companion to another publication?	☐	☐	Clear

Submit Data

Level 3 – Sorting

1. **Should this paper be included? (check all that apply)**

- ☐ YES - include this paper
- ☐ NO - not a full report of included type of study
- ☐ NO - not transplant patients
- ☐ NO - MPA not measured
- ☐ NO - health outcomes not associated with MPA measured in blood

2. **Is NO answered to any question above?**

- ☐ YES
- ☐ NO

3. **Does this study: (check all that apply)**

- ☐ provide data on the dose or dose frequency of MPA? (Review Q2a)
- ☐ specify the type of MPA given to the patient? (Review Q2b)
- ☑ describe the form of MPA measured in the blood? (Review Q3a)
- ☐ describe the time(s) MPA measurements were made? (Review Q3b)
- ☐ evaluate any factor affecting MPA monitoring? e.g. age, gender, ethnicity, use of calcineurin inhibitors, use of other medications, comorbidity (Review Q4)
- ☐ Does this study describe any economic assessment of MPA? (Review Q5)

Submit Data

Level 10 – General Data

1. Surname of first author

---

2. Year of publication

---

3. Country of study

---

4. Aim of study (<10 words or cut and paste one sentence only)

---

5. Study design

---

6. Transplanted organ(s)
Heart (Cardiac)
Kidney (Renal)
Liver
Lung
Small bowel
Other

---

7. Age (years)

Inclusion requirement

Mean for entire population
Range for entire population
Unsure
Not reported

---

8. % male in population

Entire population

Unsure
Not reported

---

9. Description of study population other than age, gender, BSA, transplanted organ

---

10. Entered into study, n =

Entire population
Condition 1
Condition 2
Condition 3
Condition 4
Unsure
Not reported

---

11. Analyzed, n =

Entire population
Condition 1
Condition 2
Condition 3
Condition 4
Unsure
Not reported

---

12. Form of MPA given

Mycophenolate mofetil (MMF, CellCept)
Mycophenolate sodium (Myfortic - enteric coated, EC - delayed release)
Other1
Other2
Unsure
Not reported

---

13. Dose of MPA given

---

14. Prospective dose adjustment planned

No
Yes - based on clinical indicators
Yes - based on MPA (or metabolite) blood levels
Unsure

---

15. Body weight or body surface area

Inclusion requirement
Mean for entire population
Range for entire population
Unsure
Not reported

---

16. Form of MPA measured

MPA
MPAG
AcMPAG
free MPA
Bound MPA
Other
Unsure
Not reported

---

17. Concomitant immuno. therapy

Cyclosporine
Tacrolimus
Methylprednisolone
Prednisone
Corticosteroids
Other1
None
Unsure
Not reported

---

18. Method of MPA measurement (provide relevant details in text box)

Pre-dose concentration
Post dose time points
Maximum concentration
Full AUC
Abbreviated AUC
Other
Unsure
Not reported

---

19. Frequency of MPA monitoring

---

20. Assay used to quantitate MPA

HPLC
EMIT
LC-MS
Other1
Unsure
Not reported

---

21. Health outcome which is related to data for MPA blood levels

1. Describe
2. Describe
3. Describe
4. Describe
5. Describe
6. Describe
7. Others

---

22. Length of follow-up

---

23. Is this paper a companion to another paper?

Yes (give RefID # if known)
Maybe (give RefID # if known)
No

24. Does this study compare outcomes for subjects

i) with planned dose adjustments based on MPA blood levels

versus

ii) subjects taking MPA without changes based on blood levels

Level 13 – Quality

1. What study design is used?

Randomized controlled trial

Non-randomized controlled trial

Observational (cohort, case-control, case series)

Other (describe)

ANSWER FOR CONTROLLED TRIALS ONLY

	YES	NO	Referred to other publication	
2. Did the authors describe a method of randomization?	☐	☐	☐	Clear
3. Did the authors describe a method of allocation concealment?	☐	☐	☐	Clear
4. Did the authors report a baseline comparison of groups?	☐	☐	☐	Clear
5. Were there differences between groups at baseline?	☐	☐	☐	Clear
6. Did the study use an intent-to-treat analysis (or did the reported results permit the calculation of intent-to-treat results)?	☐	☐	☐	Clear
7. Did the authors clearly describe the methods used to measure MPA?	☐	☐	☐	Clear
8. Did the authors clearly define the outcomes related to monitoring MPA?	☐	☐	☐	Clear
9. Were subjects blinded?	☐	☐	☐	Clear
10. Were persons measuring MPA blinded as to outcome?	☐	☐	☐	Clear
11. Were persons assessing outcomes blinded as to measures of MPA?	☐	☐	☐	Clear
12. Was there a differential loss to follow-up between groups?	☐	☐	☐	Clear

ANSWER FOR OBSERVATIONAL STUDIES ONLY (COHORT, CASE-CONTROL, CASE SERIES)

13. Was the sample size large enough to detect statistically significant differences in primary outcomes?

Yes
No

14. Was the sample size large enough to detect statistically significant differences in secondary outcomes?

Yes
No
Not applicable

15. How were study participants selected from the study population?

Consecutively
Convenience
Other (describe)
Referred to other publication
Not reported

16. Did the authors report a baseline comparison of study groups (exposure groups for cohort studies; outcome groups for case-control studies)?

Yes
No
Referred to other publication
Not applicable, study was a case series

17. Were there difference between groups at baseline?

Yes
No
Referred to other publication
Not applicable
Not reported

18. Did the authors clearly describe the methods used to measure MPA?

Yes
No
Referred to other publication

19. Did the authors clearly define the outcomes related to monitoring MPA?

Yes
No
Referred to other publication

20. Were subjects blinded?

Yes
No
Not reported

21. Were persons measuring MPA blinded as to outcome?

Yes
No
Not reported

22. Were persons assessing outcomes blinded as to measures of MPA?

Yes
No
Not reported

23. Was there a differential loss to follow-up between groups?

Yes
No
Not reported
Not applicable

24. Did the authors control for confounding?

Yes
No
Not applicable

Guide to Full Text Screening for MPA Monitoring Review

Question 1. Is this report published in English?

- If the abstract only is English, mark as 'NO'

Question 2. Is the publication a peer reviewed full report of an RCT, cohort study, case-series or case-control study (is not a case report, review, overview, discussion piece, conference report/proceeding, abstract, editorial, or letter to the editor)?

- These are study designs as defined by the Cochrane Collaboration, "The Cochrane Reviewers' Handbook Glossary"

  http://www.cochrane.org/resources/handbook/glossary.pdf

Question 3. Are subjects, humans with solid organ transplants?

- There is no age limitation for the subjects.
- There is no concomitant disorder limitation for the subjects.
- Solid organ transplants include: heart, intestines, kidney, liver, lung, pancreas.
- Islet cell transplants or any hematopoetic cell transplants are not considered solid organ transplants.

Question 4. Is any form of MPA measured in the blood?

- Metabolites that may be measured include:
  - MPA
  - mycophenolic acid
  - (UGTs). 7-*O*-MPA-glucuronide (MPAG)
  - MPA glucuronide (MPAG)
  - MPAG
  - MPA Acyl glucuronide (AcMPAG)

- Form: free or total MPA can be measured by:
  - Albumin measurement
  - Pharmacogenomics and metabolite levels
  - HPLC
  - HPLC-MS
  - EMIT
  - Other

- Method of MPA measured can include:
  - Full area under the curve (AUC)

- ❖ Trough levels
- ❖ 2-hour post dose levels
- ❖ Other

Question 5. Is any form of MPA monitored in the blood (measured with the intent of using the result for any action, based on the MPA blood level) ?

- Monitoring refers to measuring blood levels with the intention for any action based on the blood level

Question 6. Are MPA blood levels associated with any clinical health outcome?

- Clinical health outcomes include any indication of transplant rejection or adverse events

- There is a list provided for example only. There are no clinical outcomes that should not be included at this level

- Examples of clinical health outcomes are: death, re-transplantation, hepatitis, malignancy, rejection, hemodialysis, cardiac arrest or MI, bleeding, hospital stay, hospital admission, infection……

- Let in any health outcome and the clinician responsible for that section will decide if it is pertinent to the review question

Structured Format for Collecting Referee Comments

We are pleased that you have agreed to review this interim report and thank you in advance for your time. We greatly value your feedback and have provided a series of questions to collect your comments.

Please note that we are constrained to the format and style of the report as prescribed by AHRQ publication guidelines. However, within this framework, we also ask that you comment on the style and format of the report for purposes of disseminating these findings.

Thank you again for reviewing this report.

GLOBAL IMPRESSIONS

- Provide your comments on the strengths of the report or those components you valued most.
- Provide your comments on those general areas where this report can be strengthened.

SPECIFIC COMPONENTS OF THE SYSTEMATIC REVIEW

Structured Abstract

- Was it clear?

Executive Summary

- Was it clear?
- Were the clinically meaningful messages featured?

Study Identification

- Was the literature search thorough and complete?

Study Selection

- Are appropriate inclusion and exclusion criteria used to select articles?
- Are selection criteria applied in a manner that limits bias? (e.g. publication bias)

Appraisal of Studies

- Are the salient points in the literature on this topic adequately summarized and discussed?
- Are important parameters (e.g., setting, study population, study design) that could affect study results systematically addressed in text or tables?
- Is there any missing information that should be included in the text or tables?

Discussion

- Are limitations and inconsistencies of studies stated?
- Are limitations of the review process stated?
- Are implications for research discussed
- Are implications for practice discussed?

Conclusions

- Are conclusions supported by the data reviewed?
- Is evidence appropriately interpreted as indirect or inconclusive (no evidence of effect)?
- Are the recommendations valid, given the available evidence?
- Is a summary of pertinent findings provided?

OPEN COMMENTS

If there any other comments you would like to add, please do so here.

Appendix C. Evidence Tables

Evidence Table 1. General information for all included studies

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Armstrong **Year**: 2001 **Country**: Germany	**Aim**: Compare the clinical utility of the EMIT assay with HPLC for discriminating acute rejection in pediatric renal transplant recipients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 40 **Analyzed**: 40	**Population**: Pediatric renal tx; 9 patients: $\geq$ 1 acute rejection episode 31 patients: no rejection episode **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement pediatric Mean NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 600 mg/m^2 BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Methylpred. Prednisone	**Form measured**: MPA **Method of measurement**: C_o, $AUC_{(0\text{-}12h)}$, C_{max} **Frequency of MPA measure**: day 7, day 21 **Assay used**: HPLC EMIT	**Health outcome**: acute rejection **Length of followup**: 70d

Abbreviations: AcMPAG=Acyl Glucuronide metabolite of mycophenolic acid; AE=adverse effects; AE/R=adverse effects/rejection; AR=acute rejection; AUC=area-under-the-concentration-time curve; ATG= anti-thymocyte globulin; ATS=anti-thymocyte serum; AZA=azathioprine; BID=twice daily; BSA=body surface area; C_0=predose trough blood concentration; CC=concentration controlled; CL/F=total body clearance; Cmax=maximum blood or plasma concentration; Cmin=minimum blood or plasma concentration; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporin A; d=days; DGF=delayed graft function; Elisa=Enzyme-Linked ImmunoSorbent Assay; E-MPS=enteric-coated mycophenolate sodium; EMIT=enzyme-multiplied immunoassay technique; FD=fixed dose; fMPA=free mycophenolic acid; GFR=glomerular filtration rate; GI=gastrointestinal; H=high; Hb=haemoglobin; HCV=hepatitis C virus; HPLC=high-performance liquid chromatography I=intermediate; IMPDH=Iosine 5'-monophosphate dehydrogenase; IRF=impaired renal function; L=low; LSS=limited sampling strategy; MEIA II= microparticle enzyme immunoassay; Methylpred.=methylprednisolone; MMF=mycophenolate mofetil; m=months; MPA=mycophenolic acid; MPAG=mycophenolic acid glucuronide; LC-MS=liquid chromatography-mass spectrophotometry; NR=not reported; OKT3= muromonab-CD3; PK=pharmacokinetic; PSL=prednisolone; RBC=red blood cells; RCT=randomized controlled trial; ROC=receiver operating characteristic; RR=relative risk; SGOT=serum glutamic oxaloacetic transaminase; SGPT=Serum glutamic pyruvic transaminase; SIR=sirolimus; Tac=tacrolimus; TB=tuberculosis; TDM=therapeutic drug monitoring; Tmax=mean time to maximum concentration; tx=transplant; UV=ultraviolet; WBC=white blood cells; y=years

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Atcheson **Year**: 2004 **Country**: Australia	**Aim**: To investigate PK of MPA **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 42 **Analyzed**: 42	**Population**: Caucasian 98% **Organ transplanted**: Kidney (Renal) **Age**: Mean 44.3 +/- 13.1y **% Male**: 57 **Weight**: Mean 72.9 +/- 14.8 kg BMI 25.3 +/- 3.9 kg/m^2	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine n=32 Tacrolimus n=10 Simulect Diltiazem Prednisolone	**Form measured**: MPA fMPA **Method of measurement**: $AUC_{(0\text{-}6h)}$ C_o **Frequency of MPA measure**: day 5 after transplantation **Assay used**: HPLC UV and MS-MS	**Health outcome**: acute rejection GI anemia thrombo-cytopenia leucopenia **Length of followup**: 1m
Author: Barbari **Year**: 2005b **Country**: Lebanon	**Aim**: To determine MPA trough level correlation with outcomes **Comparison of monitored patients with others**: No **Study design**: Case control **Entered into study**: 30 **Analyzed**: NR	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 39y Range 20–67y **% Male**: 63.3 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g 2 times a day range 1 - 2.5 g/day **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement:** C_o **Frequency of MPA measure**: NR **Assay used**: monoclonal antibody based ELISA kit	**Health outcome**: acute rejection lymphocyte count **Length of followup**: NR

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Barbari **Year**: 2005a **Country**: Lebanon	**Aim**: To assess realtionship between clinical outcome, lymphocyte count and cyclosporine lymphocyte max level **Comparison of monitored patients with others**: No **Study design**: Case control **Entered into study**: Condition 1, graft dysfunctions: 12 Condition 2, no events: 23 **Analyzed**: NR	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: NR **Method of measurement**: NR **Frequency of MPA measure**: NR **Assay used**: NR	**Health outcome**: acute rejection **Length of followup**: NR
Author: Behrend **Year**: 1997 **Country**: Germany	**Aim**: MPA and MPAG trough levels after renal transplantation **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: 57 **Analyzed**: 48	**Population**: followup to a previously reported RCT; **Organ transplanted**: Kidney (Renal) **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day or 3 g/day; dose per body weight was 22 to 54 mg/kg; mean 83 mg/kg ± 8.4 body weight **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Corticosteroids	**Form measured**: MPA MPAG **Method of measurement**: trough levels **Frequency of MPA measure**: samples from patients varied from 4-32 **Assay used**: HPLC	**Health outcome**: graft function adverse events infections acute rejection **Length of followup**: ≥1y

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Bilbao **Year**: 2006 **Country**: Spain	**Aim**: Immunosuppression based on MMF in stable liver transplanted patients. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 56 **Analyzed**: 56	**Population**: Stable liver transplant patients **Organ transplanted**: Liver **Age**: Mean 59 +/ - 6y **% Male**: 61% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) MMF **Dose**: Initial dose of 500 mg/12h; reaching dose of 1 g each 12h for 2 weeks. **Prospective dose adjustment planned**: Yes - based on clinical indicators adjusted to tolerability and side effects **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MMF only mentioned but meant MPA **Method of measurement**: trough levels **Frequency of MPA measure**: Every 3 months for the first year, every 6 months until the 4th year then yearly until year 6. **Assay used**: NR	**Health outcome**: acute transplant rejection death progression of renal dysfunction progression of HCV recurrence mild diarrhea leucopenia de novo tumour **Length of followup**: mean 39 ± 20m; range 3 to 72m.
Author: Borrows **Year**: 2006 **Country**: UK	**Aim**: TDM of MPA associations with toxicity and rejections **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 121 **Analyzed**: 121	**Population**: Caucasian 55% South Asian 23% Afro-Carib 18% Other 4% **Organ transplanted**: Kidney (Renal) **Age**: Mean 46 +/- 9y Range 37–55y **% Male**: 58 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 750 mg BID **Prospective dose adjustment planned**: Yes - based on clinical indicators only **Concomitant medications**: Tacrolimus Methylpred. Prednisone Corticosteroids Ganciclovir (for 3m) Co-trimoxazole (for 6m) Isoniazid and pyridoxine (in Indo-Asians and previous TB) Basiliximab or Daclizumab (in 79 patients)	**Form measured**: MPA **Method of measurement**: trough levels **Frequency of MPA measure**: day 7, month 1, 3, 6, 12 **Assay used**: EMIT	**Health outcome**: acute rejection white blod cell count leucopenia thrombocytopenia bacteria/viral infection heamoglobin/anemia **Length of followup**: minimum of 12m median 25m range 13-38m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Borrows **Year**: 2005 **Country**: UK	**Aim**: To understand the determinants of MPA levels and thus aid TDM of MMF **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 117 **Analyzed**: 115 after 6m	**Population**: White 55.6% Indo-Asian 23.1 Afro-Carib 17.9% Other 3.4 **Organ transplanted**: Kidney (Renal) **Age**: Mean 46 +/- 9y Range 37-55y **% Male**: 58.1 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 250-3000 mg/day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Tacrolimus Methylpred. Prednisone	**Form measured**: MPA **Method of measurement**: C_o **Frequency of MPA measure**: week 1, 2, 3, 4, month 2-3, 4-6, 7-12, >12 **Assay used**: EMIT	**Health outcome**: diarrhea **Length of followup**: 30 m median 19m range 6 – 30m
Author: Braun **Year**: 1998 **Country**: Germany	**Aim**: Assess the relationship between therapeutic drug monitoring and clinical course in kidney and liver recipients. **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 28 **Analyzed**: 28	**Population**: patients receiving a tacrolimus based immunosuppressive regimen. **Organ transplanted**: Kidney (Renal) Liver **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 30-40 mg/kg/day **Prospective dose adjustment planned**: No **Concomitant medications**: Tacrolimus	**Form measured**: MPA **Method of measurement**: trough **Frequency of MPA measure**: Not reported **Assay used**: HPLC MEIA II	**Health outcome**: liver rejection dirrhea CMV infection G.I. symptoms **Length of followup**: median 280d range 19-585d

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Brunet **Year**: 2006 **Country**: Spain	**Aim**: To determine whether MPA monitoring is advisable in liver transplant patients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 15 **Analyzed**: day 6 n=13, day 10 n=13, day 16 n=14, month 3 n=10, month 6 n=13	**Population**: NR **Organ transplanted**: Liver **Age**: Range 29–66y **% Male**: 60 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g twice a day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Tacrolimus Methylpred. Daclizumab	**Form measured**: MPA **Method of measurement**: C_o, C_{max}, AUC_{0-12} **Frequency of MPA measure**: day 6, 10, 16 month 3, 6 **Assay used**: HPLC	**Health outcome**: diarrhea nausea **Length of followup**: 6m
Author: Brunet **Year**: 2000 **Country**: Spain	**Aim**: Compare the MPA pharmacokinetic profile and its pharmacodynamic effect on petients recieving either standard (2 g) or low (1.5 g or 1 g) MMF doses, in order to evaluate the therapeutic efficiacy of such low doses in inhibiting IMPDH activity **Comparison of monitored patients with others**: No **Study design**: Case control **Entered into study**: 27 **Analyzed**: 27	**Population**: Stable renal tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Mean 42.5 +/- 13.6 y Range 18-65y **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g, .075 g, and 0.5 g **Prospective dose adjustment planned**: No **Concomitant medications**: Prednisone CsA	**Form measured**: MPA **Method of measurement**: C_o, C_{max}, AUC_{0-12} **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: IMPDH activity **Length of followup**: 38.5m (6-166m)

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Brusa **Year**: 2000 **Country**: Italy	**Aim**: Ascertain any correlation between MPA plasma concentrations in patients receiving an oral daily dose of the drug after an allo-graft renal transplantation, and a number of variables, such as time-course, drug dosage (fixed or per body weight), frequency **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 23 **Analyzed**: 23	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Range: 18 patients 13-58y 5 patients 35-56y **% Male**: 83 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 250 to 1000 mg/day BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Corticosteroids	**Form measured**: trough **Method of measurement**: trough **Frequency of MPA measure**: once, immediately post tx OR in advanced therapy **Assay used**: HPLC	**Health outcome**: serious side effects interstitial rejection **Length of followup**: >12m
Author: Bunchman **Year**: 2001 **Country**: USA	**Aim**: To evaluate the safety, tolerability and pharmacokinetics of MMF suspension in pediatric renal recipients **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 100 **Analyzed**: 72	**Population**: 64 patients were from North America, 4 from Australia and 32 from Europe **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement 3m - 18y **% Male**: 68 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) oral suspension **Dose**: 600 mg/m2 BID up to 1 g BID **Prospective dose adjustment planned**: Yes - based on clinical indicators 49% of patients experienced adverse events that resulted in MMF dose reduction or interuption **Concomitant medications**: Cyclosporine Corticosteroids	**Form measured**: MPA MPAG **Method of measurement**: $AUC_{(0\text{-}12h)}$ **Frequency of MPA measure**: on day 7 and at 3, 9, 24 and 36 m **Assay used**: LC-MS liquid chromatography	**Health outcome**: acute rejection leucopenia diarrhea sepsis abdominal pain fever **Length of followup**: 36m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Cantin **Year**: 2002 **Country**: USA	**Aim**: To determine clinical relevance of MPA monitoring and examine its correlation with calcineurin antagonists and acute rejection **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 26 **Analyzed**: 22	**Population**: NR **Organ transplanted**: Heart (Cardiac) **Age**: Mean 54.4 +/- 14y Range 22–72y **% Male**: 73 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: Tac group: 1810 mg/day +/- 817, CsA group: 2447 +/- 896 **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Tacrolimus Corticosteroids	**Form measured**: MPA MPAG **Method of measurement**: trough levels **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: asymptomatic rejection **Length of followup**: 1y
Author: Cattaneo **Year**: 2001 **Country**: Italy	**Aim**: To optimize MMF dosing by monitoring MPA PK **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 46 **Analyzed**: 46	**Population**: adult renal tx patients **Organ transplanted**: Kidney (Renal) **Age**: Mean AUC >40 ug.ml h: 31.9 +/- 9.0y Mean AUC <40 ug.ml h: 39 +/- 12.4y Range 19-61y **% Male**: 63 **Weight**: Mean AUC >40 ug.ml h: 61.7 +/- 11.3kg, Mean AUC <40 ug.ml h: 67 +/- 12.9kg Range 44-97kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine Prednisone CsA Neoral	**Form measured**: MPA MPAG **Method of measurement**: C_0, AUC_{0-12} (as predicted by LSS AUC_{0-2}) **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: creatinine anemia **Length of followup**: 9m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Deierhoi **Year**: 1993 **Country**: USA	**Aim**: Phase I trial: to study dose ranging and side effects Rescue trial: to study MMF as rescue therapy in acute rejection **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: Condition 1: 21 phase I Condition 2: 100 quadruple therapy Condition 3: 26rescue therapy Condition 4: 39 steroid rescue **Analyzed**: Condition 1: 18 phase I Condition 2: NR quad therapy Condition 3: 25 rescue therapy Condition 4: NR steroid rescue	**Population**: 55.9% black, 2% other, 43% white **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement phase I: older than 18, rescue: older than 16 **% Male**: 54.8 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: phase I: 1500 - 3000 mg/day rescue: 2000 mg/day and 3000-3500 mg/day if no response in first week to 2000 mg **Prospective dose adjustment planned**: Yes - based on clinical indicators side effects - phase I: diarrhea, rescue: diarrhea and nausea **Concomitant medications**: Cyclosporine phase I and rescue Methylpred. phase I Prednisone rescue Corticosteroidsphase I phase I and rescue: Minnesota antilymphocyte globulin(MALG) rescue: azathioprine	**Form measured**: MPA **Method of measurement**: trough levels, peak concentration **Frequency of MPA measure**: Day 1, 7, 14, 20 **Assay used**: HPLC	**Health outcome**: diarrhea - phase 1 and rescue nausea - phase 1 and rescue elevated liver enzymes - phase 1 **Length of followup**: phase I trial: mean 26m range 22 - 28m rescue: mean 20m range 16 - 24m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: DeNofrio **Year**: 2000 **Country**: USA	**Aim**: To determine the clinical significance of MPA concentrations following orthotopic heart transplantation (OHT) **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 38 **Analyzed**: 38	**Population**: Tx patients with surveillance biopsy **Organ transplanted**: Heart (Cardiac) **Age**: Mean 53 +/- 10y **% Male**: 82 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine	**Form measured**: MPA fMPA **Method of measurement**: C_o, C_{max}, AUC_{0-12} (as predicted by LSS C_o, C_{20}, C_{40}, C_{75}, C_{120}) **Frequency of MPA measure**: once on MMF **Assay used**: HPLC	**Health outcome**: rejection cardiac allograft **Length of followup**: 310 ±278d
Author: Dipchand **Year**: 2001 **Country**: Canada	**Aim**: Review our experience with MMF dosing and the role of MPA levels for therapeutic drug monitoring in a population of pediatric heart transplant recipients **Comparison of monitored patients with others**: No **Study design**: Retrospective Cohort **Entered into study**: 44 **Analyzed**: 44	**Population**: Pediatric heart tx **Organ transplanted**: Heart (Cardiac) **Age**: Range 29d-23.5y Median 6.3y **% Male**: 61 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: various: 15-159 mg/kg **Prospective dose adjustment planned**: required based on clinical indicators **Concomitant medications**: Cyclosporine (A or neural) Tacrolimus Corticosteroids azathiaprine ATG OKT3 ATS	**Form measured**: MPA **Method of measurement**: Trough **Frequency of MPA measure**: various: 1-7 levels **Assay used**: EMIT	**Health outcome**: rejection **Length of followup**: 8w

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Filler **Year**: 2000 **Country**: Germany	**Aim**: Replacing Aza with MMF in long term renal transplant recipients with evidence of CsA toxicity, thus allowing a safer reduction of CyA without an increased risk of rejection. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 18 **Analyzed**: 18	**Population**: Pediatric and adolescent renal tx recipients with chronic CyA toxicity **Organ transplanted**: Kidney (Renal) **Age**: Mean 17.2 y $\pm$ 4.3 SDy **% Male**: 50 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 600 mg/m2 BID **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine Steroids Azathioprine(13 patients but weaned off in 2) ATG-induction (5 patients) Tacrolimus (1 patient due to resistance but weaned off soon after due to side effects)	**Form measured**: MPA **Method of measurement**: C_o $AUC_{(0-12)}$ **Frequency of MPA measure**: all = 21 days +/- 17; 1 to 4 profiles **Assay used**: HPLC EMIT	**Health outcome**: leucopenia thrombocytopenia diarrhea **Length of followup**: Mean 6.2 $\pm$ 2.7y Range 2.3-11.8y

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Filler **Year**: 1998 **Country**: Germany	**Aim**: MMF with Tac for steroid-resistant vascular rejection in pediatric renal allografts **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 7 **Analyzed**: 7	**Population**: Adolescent renal transplant recipients having an acute rejection episode. **Organ transplanted**: Kidney (Renal) **Age**: Mean 15.8 +/- 1.6y Range 13 - 18y **% Male**: 29% **Weight**: Not reported	**Form given**: Mycophenolate mofetil (MMF, CellCept) MMF **Dose**: 600 mg/m2 BID reduced to 320 mg/m2 /day over 7 wks **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels trough concentrations were used to adjust MMF doses **Concomitant medications**: Tacrolimus Methylpred.	**Form measured**: MPA MPAG **Method of measurement**: C_0 AUC_{0-12} **Frequency of MPA measure**: Repetetive blood sampling from before dose and then 9 more times after dosage in the next 12 hours. Drug monitoring was performed by the estimation of trough concentration and pharmacokinetic profile between days 10 and 18. **Assay used**: HPLC	**Health outcome**: renal graft losses severe diarrhea **Length of followup**: range 49-503d, mean 282d
Author: Flechner **Year**: 2005 **Country**: USA	**Aim**: To determine efficacy & side effects of low dose (1 g) MMF in a CNI drug avoidance regimen including sirolimus/steroids **Comparison of monitored patients with others**: Yes versus clinically driven dose changes **Study design**: Prospective Cohort **Entered into study**: Condition 1 160 Condition 2 100 **Analyzed**: Condition 1 160 Condition 2 100	**Population**: White 79%, Black 18%, Others 3% **Organ transplanted**: Kidney (Renal) **Age**: Mean 48.5 **% Male**: 66.5 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID (n=160) and 500 mg BID (n=100) **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Methylpred. Basiliximab Sirolimus Diltiazem Thymoglobulin	**Form measured**: MPA **Method of measurement**: Co level **Frequency of MPA measure**: At 2wks, 1m , 3m and 6m **Assay used**: HPLC	**Health outcome**: Acute rejections CMV infections Polyoma (BK) viral infections GI complaints Nausea/ vomitting/ dyspepsia, abdomenal pains, and diarrhea. **Length of followup**: 6m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Gajarski **Year**: 2004 **Country**: USA	**Aim**: To determine correlation between MMF dose and MPA level and impact on rejection among young cardiac receipients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 26 **Analyzed**: 26	**Population**: 16 children, 10 adults **Organ transplanted**: Heart (Cardiac) **Age**: Mean 15.4 +/- 9.5y Range 1 m-33y **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: average 1206.8 +/- 301.9 mg/m2 and 37.9 +/- 12.5 mg/kg **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MPA MPAG **Method of measurement**: C_o **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: biopsy grades **Length of followup**: NA
Author: Gonzales-Roncero **Year**: 2005 **Country**: USA	**Aim**: To determine the effects of renal insufficiency on PK of MMF **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: Condition 1 10 Condition 2 10 control **Analyzed**: Condition 1 10 Condition 2 10 control	**Population**: Cadaveric donor renal tx patients **Organ transplanted**: Kidney (Renal) **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: group I: 185 +/- 0.2 g/day group II: 1.7 +/- 0.5 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine	**Form measured**: MPA MPAG free MPA **Method of measurement**: $AUC_{(0\text{-}12h)}$ **Frequency of MPA measure**: 0, 20, 40, 75 minutes 1, 2, 3, 4, 6, 8, 10, 12 hours after MMF dose **Assay used**: HPLC/UV	**Health outcome**: renal insufficiency **Length of followup**: >1y

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Grasser **Year**: 2001 **Country**: Austria	**Aim**: Present a nonblinded, nonrandomized long-term followup study to evaluate MPA trough level measurement for the quidance of MMF rejection prophylaxis after Liver TX. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 11 **Analyzed**: 10	**Population**: adult liver tx recipients **Organ transplanted**: Liver **Age**: Mean 56y Range 27-70y **% Male**: 73 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: NR: Target concentration = 1ug/mL **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Methylpred. Orednisone horse ATG Apredisolone	**Form measured**: MPA **Method of measurement**: trough **Frequency of MPA measure**: daily for 2 weeks, then every other week **Assay used**: EMIT	**Health outcome**: SGOT SGPT Bilirubin Leucopenia **Length of followup**: 6m
Author: Hale **Year**: 1998 **Country**: Netherlands, Belgium	**Aim**: Confirm the observed pharmacokinetic-pharmacodynamic relationship by studying the relationship between MPA PF and the likelihood of rejection **Comparison of monitored patients with others**: Three target MPA AUC values compared **Study design**: RCT **Entered into study**: Condition 1 L: 51 Condition 2 I: 47 Condition 3 H: 52 **Analyzed**: Condition 1 L:29 Condition 2 I: 28 Condition 3 H: 20	**Population**: Recipients of 1st or 2nd kidney; 140 of 150 were caucasian **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement > 18y Range L: 47.8 +/- 11.5; I: 46.9 +/- 13.8; H: 50.6 +/- 10.5 **% Male**: L: 58.8; I: 63.8; H: 59.6 **Weight**: L: 69.8 +/- 12.5 I: 65.9 +/- 13/1 H: 67.4 +/- 11.3	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: L: 0.45 g BID then adj I: 0.95 g BID then adj H: 1.7 g BID then adj **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Corticosteroids Prednisone	**Form measured**: MPA **Method of measurement**: C_o C_{max} AUC_{0-12} **Frequency of MPA measure**: day 3,7,11,21,28 week 8,12,16,20 **Assay used**: HPLC	**Health outcome**: Acute rejection adverse events (vomit, abdominal pain, diarrhea, leukopenia, pneumonia) **Length of followup**: 6m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Hazzan **Year**: 2005 **Country**: France	**Aim**: To compare incidence of acute rejection after withdrawal from CsA or MMF **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: CsA group: 54 MMF group: 54 **Analyzed**: CsA group: 54 MMF group: 54	**Population**: BMI CsA group 23.3 +/- 3.9, MMF group 24.0 +/- 11.2 **Organ transplanted**: Kidney (Renal) **Age**: Mean CsA group 42.5 +/- 12.1 MMF group 45.1 +/- 11.2 **% Male**: 63 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: *CsA group* MMF dose = 1.93 +/- 0.2 then withdrawn to 0, *MMF group* MMF dose = 1.99 +/- 0.1 **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: $AUC_{(0\text{-}12)}$ C_0 **Frequency of MPA measure**: Once at 3 m **Assay used**: Enzyme	**Health outcome**: acute rejection **Length of followup**: 1y
Author: Heller **Year**: 2007 **Country**: Germany	**Aim**: Study the relation of plasma concentrations of AcMPAG and MPAG with the incidence of diarrhea **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 290 **Analyzed**: 290	**Population**: **Organ transplanted**: Kidney **Age**: 53.4y **% Male**: 62 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: Fixed Dose group: 1 g BID, Controlled Concentration group: target concentration of 30-60 mg*h/L **Prospective dose adjustment planned**: Yes, based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MPA, MPAG, AcMPAG **Method of measurement**: Abbreviated AUC (0, 30m, 2h) **Frequency of MPA measure**: Day 3, 10, week 4, months 3, 6 and 12 **Assay used**: HPLC initially then later, LC-MS	**Health outcome**: Diarrhea **Length of followup**: 12m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Hesse **Year**: 2001 **Country**: Netherlands	**Aim**: To evaluate the need for routine monitoring of MPA trough plasma levels to prevent acute rejection in heart transplant recipients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 20 **Analyzed**: 20	**Population**: NR **Organ transplanted**: Heart (Cardiac) **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1500 mg BID + dose reductions on clinical symptoms **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Tacrolimus Prednisone CsA	**Form measured**: MPA **Method of measurement**: C_o **Frequency of MPA measure**: at biopsy **Assay used**: EMIT	**Health outcome**: acute rejection biopsy score **Length of followup**: Mean 10.1m
Author: Hubner **Year**: 2000 **Country**: Germany	**Aim**: To determine the relationship between MMF side effects and MPA trough levels in renal transplant patients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 30 **Analyzed**: 30	**Population**: adult renal tx recipient **Organ transplanted**: Kidney (Renal) **Age**: Mean 45y **% Male**: 66.7 **Weight**: Mean for entire population mean body weight 73 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1.0 g twice a day **Prospective dose adjustment planned**: Yes - based on clinical indicators adverse events **Concomitant medications**: Cyclosporine Methylpred.	**Form measured**: MPA **Method of measurement**: Predose concentration **Frequency of MPA measure**: 3-4 times a wk for the first month, once a wk during the second month and once a month thereafter **Assay used**: EMIT	**Health outcome**: acute rejection leucocyte count other adverse reactions (cytomegalo virus infection, pneumonia, urinary tract infection, herpes zoster, infected hematoma, pancreatitis, leucopenia) **Length of followup**: NR

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Johnson **Year**: 1999 **Country**: Australia	**Aim**: To determine whether MPA kinetics vary after renal trasplantation and to examine the potenial role of enterohepatic recirculation. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 10 **Analyzed**: 10	**Population**: consecutive kidney transplant recipients **Organ transplanted**: Kidney (Renal) **Age**: Mean 41.7 +/- 5.0y **% Male**: 60 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Methylpred. ranitidine sulfamethoxazole/trimethoprim iron supplements amphotericin lozenges diltiazem calcitrol	**Form measured**: MPA MPAG **Method of measurement**: $AUC_{(0\text{-}12H)}$ tmax array of limited sampling **Frequency of MPA measure**: day 2, 5, 28 **Assay used**: HPLC	**Health outcome**: creatinine albumin **Length of followup**: 28d
Author: Johnson **Year:** 1998 **Country:** USA	**Aim**: The purpose of this study was to determine the effect of renal function on the elimination and disposition of MPA and its MPAG after oral administration of the pro-drug MMF,and to examine hemodialysis removal of MPA and its MPAG. **Comparison of monitored patients with others**: No **Study design**: Case control **Entered into study**: 31 **Analyzed**: 31	**Population**: Patients with varing degree of renal function **Organ transplanted**: Kidney (Renal) **Age**: 44.5 +/- 15.9, 41.7+/- 10.3, 43.8 +/- 10.8, 45.3 +/- 15.0, 45.3 +/- 8.5 respectively in Groups1-5 **% Male**: 74 83.3, 66.6, 100, 57.1,66.6 respectively in Groups 1-5 **Weight**: 80.2 +/- 10.3, 74.9 +/- 15.6, 103.7 +/- 31.2, 81.8 +/- 19.0, and 72.7 +/- 12.1 respectively in groups 1-5	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g **Prospective dose adjustment planned**: No **Concomitant medications**: None	**Form measured**: MPA, MPAG **Method of measurement**: Maximum concentration, Full $AUC_{(0\text{-}24h)}$ and $AUC_{(0\text{-}96h)}$ **Assay used**: HPLC **Frequency of MPA measure**: 24 h and 96 h after administration	**Health outcome**: elimination and disposition of MPA and its MPAG, Hemodialysis removal of MPA and its MPAG **Length of followup:** 96h

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Kaplan **Year**: 1999 **Country**: USA	**Aim**: To examine the protein binding and free concentrations of MPA in 23 adult renal transplant patients, 8 of whom had chronic renal insufficiency **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 23 **Analyzed**: 23	**Population**: 23 Renal transplant recipients; 8 with chronic renal insufficiency **Organ transplanted**: Kidney (Renal) **Age**: Range 46.7 +/- 9.2 y for chronic renal subjects 43.3 +/- 8.6 For renal patients without chronic insufficiency **% Male**: 37.5 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1.75 +/- 0.3 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: NR	**Form measured**: MPA MPAG fMPA **Method of measurement**: abbreviated AUC_{0-12} (based on LSS of $C_{0,}$ $C_{20,}$ $C_{40,}$ $C_{75,}$ C_{120}) **Frequency of MPA measure**: once (>2wk) **Assay used**: HPLC	**Health outcome**: adverse events leucopenia abdominal pain **Length of followup**: >2w
Author: Kiberd **Year**: 2004 **Country**: Canada	**Aim**: To examine whether early exposure to MPA predicts later outcomes **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 94 **Analyzed**: day 3: 94, day 5: 86, day 7: 58	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 48 +/- 13y **% Male**: 70 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day fixed **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Prednisone Neoral	**Form measured**: MPA **Method of measurement**: C_0 C_2 AUC_{0-12} (as predicted by LSS of $C_{0,}$ $C_{1,}$ $C_{2,}$ C_4) **Frequency of MPA measure**: day 3, 5, 7 and up to 3m **Assay used**: HPLC	**Health outcome**: acute rejection toxicity **Length of followup**: 3m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Kreis **Year**: 2000 **Country**: 14 European centres	**Aim**: Evaluate the clinical activity and safety of sirolimus in association with MMF and steriods compared with CsA-MMF steroid therapy in human renal transplantation **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: Condition 1 SIR: 40 Condition 2 CsA: 38 **Analyzed**: Condition 1 SIR: 40 Condition 2 CsA: 38	**Population**: First renal tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Range for entire population SIR: 43.5 +/- 10.9 (22-62); CsA: 42.9 +/- 11.4 (18-60) **% Male**: Entire population SIR: 70; CsA: 71 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Corticosteroids Sirolimus	**Form measured**: MPA **Method of measurement**: trough **Frequency of MPA measure**: weekly **Assay used**: EMIT	**Health outcome**: trough VS rejection **Length of followup**: 6m
Author: Krumme **Year**: 1998 **Country**: Germany	**Aim**: Whether blood levels of MPA have an impact on the outcome after renal transplantation, such as on the incidence of acute rejection as well as on the incidence of infection **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 48 **Analyzed**: 48	**Population**: Consecutive renal tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Range 46 +/-11y **% Male**: 71 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: Yes based on MPA plasma levels and clinical indicators **Concomitant medications**: Cyclosporine Methylpred.	**Form measured**: MPA **Method of measurement**: trough levels **Frequency of MPA measure**: 6 to 24 samples/ patient **Assay used**: EMIT	**Health outcome**: rejection infection urinary infection **Length of followup**: 2m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Kuriata - Kordek **Year**: 2002 **Country**: Poland	**Aim**: To investigate the realtionship between PK of MPA and risk of developing adverse events or acute rejection **Comparison of monitored patients with others**: No **Study design**: Case control **Entered into study**: Condition I: 12 patients with acute rejection Condition II: 27 patients without acute rejection **Analyzed**: NR	**Population**: all adult kidney tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement group I: 38.12 +/- 9.5 y, group II: 38.52 +/- 9.21y **% Male**: 38.5 **Weight**: Group I: 68.46 +/- 11.23, Group II: 62.89 +/- 12.41	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2.0 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: C_0, C_{40}, C_{60}, C_{120}, C_{max} **Frequency of MPA measure**: 14 days - 12 months **Assay used**: HPLC	**Health outcome**: acute rejection side effects leucopenia anemia GI symptoms **Length of followup**: 12m
Author: Kuypers **Year**: 2004 **Country**: Belgium	**Aim**: To examine whether the PK parameter of tac and MPA reflect their clinical efficacy **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 100 **Analyzed**: NR	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean for entire population median 51.5y **% Male**: 59 **Weight**: Mean 69.2 +/- 13.1 kg at baseline	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 0.5 g BID or 1 g BID **Prospective dose adjustment planned**: Yes based on clinical indicators **Concomitant medications**: Tacrolimus Methylpred. Daclizumab	**Form measured**: MPA **Method of measurement**: C_o C_{max} AUC_{0-12} **Frequency of MPA measure**: day 7, 42, 90, 180, 360 and month 3, 6, 12 **Assay used**: EMIT	**Health outcome**: acute rejection infection leucopenia anemia **Length of followup**: 12m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Kuypers **Year**: 2003b **Country**: Belgium	**Aim**: To identify a possible relation between PK of MPA adn clinical outcomes **Comparison of monitored patients with others**: No **Study design**: Non-randomized controlled trial **Entered into study**: 33 **Analyzed**: 33	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 49.4 +/- 13.1y **% Male**: 57.6 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Tacrolimus Daclizumab Methylpredisolone	**Form measured**: MPA MPAG AcMPAG fMPA **Method of measurement**: C_0, C_{max}, AUC_{0-12} (as predicted by LSS of C_0, C_{40m}, C_{2h}) **Frequency of MPA measure**: day 3, 7, 10, 14, 28, week 6, 8, 10, 12, 14, month 4,6, 9, 12 **Assay used**: HPLC	**Health outcome**: rejection diarrhea leucopenia anemia **Length of followup**: 12m
Author: Kuypers **Year**: 2003a **Country**: Belgium	**Aim**: To assess whether long term changes in MPA exposure and Tac and corticosteroids are dose dependent and not reflected through plasma concentration **Comparison of monitored patients with others**: No **Study design**: Non-randomized controlled trial **Entered into study**: 100 **Analyzed**: NR	**Population**: >17 and received a primary or secondary cadaberic donor kidney **Organ transplanted**: Kidney (Renal) **Age**: Mean for entire population meidan 51.5y **% Male**: 59 **Weight**: Mean 69.2 +/- 13	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g/day or 2 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Methylpredisolone Tacrolimus Daclizumab (31 patients)	**Form measured**: MPA **Method of measurement**: C_0, C_{max}, AUC_{0-12} **Frequency of MPA measure**: day 7, week 6, month 3 and 12 **Assay used**: EMIT	**Health outcome**: biopsy proven rejection survival diarrhea **Length of followup**: 12m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Le Meur **Year**: 2007 **Country**: France	**Aim**: Trial of recipients randomized to receive either FD MMF or a CC regimen in which MMF dose adjustments were calculated to reach predefined MPA target levels **Comparison of monitored patients with others**: Yes, versus predetermined dosage schedule **Study design**: RCT **Entered into study**: CC: 70 FD: 67 **Analyzed**: CC: 65 FD: 65	**Population**: Consecutive recipients of a first or second allograft **Organ transplanted**: Kidney **Age**: CC group: 50 +/- 14 FD group 49 +/- 13 **% Male**: CC group: 71 FD group 58 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: FD: 1 g BID CC: Days 1-7, 1 g BID, then target dose = 40 mg*h/L **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Methylpred. Basiliximab Trimethoprim-sulfamethoxazole	**Form measured**: MPA **Method of measurement**: Abbreviated AUC: 20m, 1h, 3h **Frequency of MPA measure**: Days 7, 14, months 1, 3, 6, 12 **Assay used**: HPLC	**Health outcome**: Treatment failure (composite of death, graft loss, acute refection and MMF discontinuation) Acute rejection Adverse events **Length of followup**: 12m
Author: Lu **Year**: 2005 **Country**: China	**Aim**: To assess influence of CsA and Tac on MPA and correlate PK parameters, patient characteristics and clinical outcomes **Comparison of monitored patients with others**: No **Study design**: Non-randomized clinical trial **Entered into study**: 29 **Analyzed**: 29	**Population**: Chinese recipients of a 1st kidney **Organ transplanted**: Kidney (Renal) **Age**: Mean 40.0 +/- 12.0y **% Male**: 58.6 **Weight**: Mean 58.0 +/- 10.0 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1000 mg BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone Tacrolimus	**Form measured**: MPA **Method of measurement**: $AUC_{(0\text{-}12h)}$ **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: acute rejection **Length of followup**: 1m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Lu **Year**: 2006 **Country**: China	**Aim**: To investigate the relationship between clinical events and the PK of MPA in adult renal transplant patients. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 37 **Analyzed**: 37	**Population**: first cadaveric renal transplantation **Organ transplanted**: Kidney (Renal) **Age**: Mean 34.1 + - 7.1y Range 18 to 64y **% Male**: 65% **Weight**: Inclusion requirement	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: weight directed dosage (50 kg: 2.0 g/day) starting 2 days before transplantation **Prospective dose adjustment planned**: Yes - based on clinical indicators dose adjusted according to drug tolerance and related side effects **Concomitant medications**: Cyclosporine CsA, Neoral steroids	**Form measured**: MPA **Method of measurement**: C_o C_{max} C_{60} AUC_{0-12} **Frequency of MPA measure**: MMF PK profiles from 0 (predose or Cmin), 0.4 (C 30), 1 (C60). 1.5, 2, 2.5, 4, 6, 8, 10, 12 hour samples. MMF trough concentrations measured before MMF dosage on day 4, 7, 21, & 28 as well as 1.5, 2, 3, and 6 months. **Assay used**: HPLC ROC curve analysis	**Health outcome**: acute rejection (biopsy proven) infection in different organs with various pathogens, hematologic events, mainly leukopoenia and thrombo-cytopenia, GI symptoms, none of which were severe diarrhea **Length of followup**: 6m
Author: Lu **Year**: 2004 **Country**: China	**Aim**: To investigate relation between clinical events and PK of MPA in Chinese kidney transplant recipients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 22 **Analyzed**: 22	**Population**: Adults of first cadaver kidney tx **Organ transplanted**: Kidney (Renal) **Age**: Mean 36 +/- 7.1y Range 18-57y **% Male**: 54.5 **Weight**: Not reported	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: weight directed 50 kg 2 g/day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine	**Form measured**: MPA **Method of measurement**: Predose concentration $AUC_{(0-12h)}$ **Frequency of MPA measure**: 2 days before transplant, 14 days after transplant **Assay used**: HPLC RP-HPLC	**Health outcome**: toxicity acute rejection **Length of followup**: 6m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Maes **Year**: 2003 **Country**: Belgium	**Aim**: To explore GI tract in MMF treated patients with diarrhea **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 26 **Analyzed**: 26	**Population**: Transplant recipients with persistent afebrile diarrhea **Organ transplanted**: Kidney (Renal) **Age**: Mean 46 +/- 15y Range 18 – 70y **% Male**: 46.2 **Weight**: Mean 66.8 +/- 13.8	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1.6 +/- 0.5 g/day, range 1 – 3 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Tacrolimus Methylpred.	**Form measured**: MPA MPAG AcMPAG free MPA **Method of measurement**: C_o **Frequency of MPA measure**: NR **Assay used**: NR	**Health outcome**: bile acid malabsorption colonic transit time infection **Length of followup**: 2y
Author: Mandla **Year**: 2006 **Country**: Norway	**Aim**: TDM of MPA with CsA ar Tac was investigated in renal tx patients **Comparison of monitored patients with others**: No **Study design**: Non-randomized Controlled Trial **Entered into study**: Condition 1 68 CsA Condition 2 10 Tac **Analyzed**: 78	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 54y Range 19 -77y **% Male**: 73.1 **Weight**: Mean 74 kg Range 49-139	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g 2 times day in combined kidney plus pancreas transplant patients 1 g 3 times a day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine Tacrolimus Methylpred. Prednisone	**Form measured**: MPA MPAG **Method of measurement**: Predose concentration **Frequency of MPA measure**: 2-3/wk for first 4 wks, then 1-2/wk up to 3 months **Assay used**: HPLC Automated sequential trace enrichment of dialysis	**Health outcome**: acute rejection **Length of followup**: 3m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Meiser **Year**: 1999a **Country**: Germany	**Aim**: To investigate the efficacy of Tac and MMF combination therapy as primary immunosupression. **Comparison of monitored patients with others**: Phase I, fixed dose patients compared to phase II, patients with dose adjusted for MPA level **Study design**: Non-randomized Controlled Trial **Entered into study**: Condition 1 Phase I 15 Condition 2 Phase II 30 **Analyzed**: Condition 1 Phase 1 15 Condition 2 Phase II 30	**Population**: Consecutive patients undergoing primary orthotopic cardiac transplantation **Organ transplanted**: Heart (Cardiac) **Age**: Inclusion requirement >18y Mean Phase I 50.6 +/- 11.4, Phase II 54.01 +/- 8.9 Range Phase I 18-64, Phase II 21-66 **% Male**: Phase I 87%, Phase II 77% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: Phase I 1 g BID, Phase II target level 2.5 to 4.5 ug/mL **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels Phase II **Concomitant medications**: Tacrolimus Methylpred. Prednisone	**Form measured**: MPA **Method of measurement**: C_0 **Frequency of MPA measure**: Daily X 3 weeks, then biweekly **Assay used**: EMIT	**Health outcome**: rejection survival **Length of followup**: Phase I: 522 (432-616)d, Phase II: 273 (133-388)d

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Meiser **Year**: 1999b **Country**: Germany	**Aim**: Assess the efficacy of Tac and mycophenolate as primary therapy following cardiac transplantation **Comparison of monitored patients with others**: Phase I, fixed dose patients compared to phase II, patients with dose adjusted for MPA level **Study design**: Non-randomized Controlled Trial **Entered into study**: Condition 1 PhaseI: 15 Condition 2 Phase II: 30 **Analyzed**: Condition 1 Phase I: 15 Condition 2 Phase II: 30	**Population**: consecutive patients undergoing orthotopic cardiac transplantations **Organ transplanted**: Heart (Cardiac) **Age**: Inclusion requirement Phase I & II: >18y Range Phase I: 50.6 +/- 11.4 (18-64); Phase II: 54.1 +/- 8.9 (21-66) **% Male**: Phase I: 87; phase II: 77 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: Phase I: 1 g/day BID Phase II: 2.5 to 4.5 ug/ml **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels Phase II **Concomitant medications**: Tacrolimus Prednisone Methylpred.	**Form measured**: MPA **Method of measurement**: C_o **Frequency of MPA measure**: Phase I: NR Phase II: Monthly **Assay used**: EMIT	**Health outcome**: rejection toxicity **Length of followup**: Phase I: 696 $\pm$ 62d (606-790) Phase II: 436 $\pm$ 88d (175-562)
Author: Merkel **Year**: 2005 **Country**: Germany	**Aim**: To use MMF to prevent rejection in renal transplant patients **Comparison of monitored patients with others**: No **Study design**: Retrospective Cohort **Entered into study**: 35 **Analyzed**: 35	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 44 +/- 13.6y Range 13– 63y **% Male**: 68.6 **Weight**: Mean 72.9 +/- 14.3 Range 47-104	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 0.5-1.0 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone Corticosteroids	**Form measured**: MPA MPAG **Method of measurement**: trough levels **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: acute rejection drug reactions (diarrhea) **Length of followup**: 16m, mean 5.7m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Morgera **Year**: 1998b **Country**: Germany	**Aim**: MMF PK in renal transplant recipients on peritoneal dialysis. **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: Condition 1 delayed graft function n=3 Condition 2 recovering renal function n=2 **Analyzed**: Condition 1 delayed graft function n=3 Condition 2 recovering renal function n=2	**Population**: Early post transplant patients on dialysis **Organ transplanted**: Kidney (Renal) **Age**: Range 25 – 60y **% Male**: 20% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID; Two 12 hour periods, once before and once after peritoneal dialysis. **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Methylpred. Oxacillin	**Form measured**: MPA MPAG **Method of measurement**: NR **Frequency of MPA measure**: Before and 8 times after dosage in 12 hour period **Assay used**: HPLC semi-automatic	**Health outcome**: GFR **Length of followup**: 2d
Author: Morgera **Year**: 1998a **Country**: Germany	**Aim**: PK of MMF in renal transplant patients on dialysis **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: Condition 1 delayed graft function n=3 Condition 2 recovering graft function n=2 **Analyzed**: Condition 1 delayed graft function n=3 Condition 2 recovering graft function n=2	**Population**: Early post transplant patients on dialysis **Organ transplanted**: Kidney (Renal) **Age**: Range 25 to 60y **% Male**: 20% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID; Two 12 hour periods, once before and once after peritoneal dialysis. **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Methylpred. Oxacillan	**Form measured**: MPA MPAG **Method of measurement**: NR **Frequency of MPA measure**: before and 8 times after dosage in 12 hour period **Assay used**: HPLC	**Health outcome**: GFR **Length of followup**: 2d

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Mourad **Year**: 2001b **Country**: Belgium	**Aim**: Assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship for MPA in kidney transplant patients recieving low-dose MMF (500 mg twice a day) in combination with Tac. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 51 **Analyzed**: 51	**Population**: Adult, kid tx on low dose MPA **Organ transplanted**: Kidney (Renal) **Age**: Range 32-68y Median 49y **% Male**: 57 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 500 mg BID + adjustment for side effects **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Tacrolimus Corticosteroids	**Form measured**: MPA **Method of measurement**: **Frequency of MPA measure**: Immediate stabilized if side effect or rejected + 3m **Assay used**: EMIT	**Health outcome**: rejection side effects thrombo-cytopenia esophagitis lecopenia anemia GI symptoms Diarrhea **Length of followup**: 3m
Author: Mourad **Year**: 2001a **Country**: Belgium	**Aim**: Investigate the relationship between the clinical events and the PK of MPA in adult renal transplantation **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 31 **Analyzed**: 31	**Population**: Adult kidney tx **Organ transplanted**: Kidney (Renal) **Age**: Mean 43y Range 16-67y **% Male**: 55 (17/31) **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine anti-thymocyte globulin steroids	**Form measured**: MPA **Method of measurement**: Co, C_{30m}, AU_{C0-12} **Frequency of MPA measure**: early after tx, 3 months and at every clinical event **Assay used**: EMIT HPLC	**Health outcome**: side effects rejection esophagitis leucopenia diarrhea anemia thrombo-cytopenia **Length of followup**: 3m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Mourad **Year**: 2000 **Country**: Belgium	**Aim**: Evaluate the analytical performances of this new EMIT assay, to determine the main PK parameters of MPA in renal transplantation, and finally, to evaluated a possible relationship between pharmacodynamics and pharmacokinetics of MPA (correlation) **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 7 **Analyzed**: 7	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 46y Range 33-57y **% Male**: 29 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine prednisolone	**Form measured**: MPA **Method of measurement**: C_{0}-AUC_{0-12}, **Frequency of MPA measure**: week 1,4,12 **Assay used**: EMIT	**Health outcome**: acute rejection side effects **Length of followup**: 12w
Author: Mudge **Year**: 2004 **Country**: Australia	**Aim**: To study the effect of iron on MMF absorption in renal transplant patients **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: 45 **Analyzed**: 40	**Population**: white 98%, BMI 25.1 +/- 3.7 kg/m2; only adults **Organ transplanted**: Kidney (Renal) **Age**: Mean 45.2 +/- 13.2y **% Male**: 55 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Tacrolimus Prednisone	**Form measured**: MPA **Method of measurement**: AUC_{0-12} (as predicted by LSS of C_{0}, C_{1}, C_{3}, C_{6}) **Frequency of MPA measure**: day 5 **Assay used**: HPLC	**Health outcome**: acute rejection toxicity GI symptoms **Length of followup**: 7m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Naesens **Year**: 2006 **Country:** Belgium	**Aim**: To determine the relationship between single nucleotide polymorphisms in the MRP2 genes and MPA PK **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: Condition 1 MRP2 carriers 41 Condition 2 MRP2 non carriers 54 **Analyzed**: Condition 1 MRP2 carriers 41 Condition 2 MRP2 non carriers 54	**Population**: caucasian de novo renal allograft recipients **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement >17 Mean 51.3 +/- 14.1y **% Male**: 60 **Weight**: Mean 68.7 +/- 13.4 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 0.5 or 1 g BID **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Tacrolimus Corticosteroids Daclizumab for 29 subjects Oral Methylpred.	**Form measured**: MPA **Method of measurement**: CL/F apparent steady-state total body clearance **Frequency of MPA measure**: day 7(12 hour AUC),day 42(2 hour AUC),day 90(4 hour AUC),day 360(4 hour AUC) **Assay used**: EMIT	**Health outcome**: liver dysfunction **Length of followup**: 360d
Author: Naito **Year**: 2006 **Country**: Japan	**Aim**: To obtain information on PK of MPA/MPAG and their interactions with CNIs **Comparison of monitored patients with others**: No **Study design**: Non-randomized Controlled Trial **Entered into study**: 9 in Tac group, 3 in CNI group, 13 in CsA group **Analyzed**: NR	**Population**: Japanese renal tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Range 14 – 60y **% Male**: 64 **Weight**: Mean 59.2 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 250-1750 mg/day **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MPA MPAG **Method of measurement**: correlation between MMF dose Blood Co Regression analysis **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: serum creatinine **Length of followup**: >6m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Okamoto **Year**: 2005 **Country**: Japan	**Aim**: To analyze usefulness of monitoring MPA to optimize therapy **Comparison of monitored patients with others**: No **Study design**: Non-randomized Controlled Trial **Entered into study**: 67 **Analyzed**: Entire population 67 (PK studies of MPA performed in 46 patients)	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 38 +/- 14y **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 25 mg/kg initially, then adjusted afterwards **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels and on adverse events and TDM **Concomitant medications**: Cyclosporine n=35 Tacrolimusn=32	**Form measured**: MPA **Method of measurement**: $C_{0,}$, AUC_{0-9} **Frequency of MPA measure**: 2 weeks and 4 weeks after transplant **Assay used**: EMIT 2000	**Health outcome**: acute rejection infection GI **Length of followup**: NR
Author: Orlando **Year**: 2006 **Country**: Italy	**Aim**: Increase 1.5 g/day MMF to 2 g/day in patients with CNI chronic toxicity. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 42 **Analyzed**: 41	**Population**: Adult liver transplanted patients with CNI related adverse effects. **Organ transplanted**: Liver **Age**: Mean 60.1y Range 35 – 67y **% Male**: 81% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) MMF **Dose**: 250 mg per os BID increased weekly by 500 mg to dose of 1500 mg/day **Prospective dose adjustment planned**: Yes - based on clinical indicators With a diagnosis of AR then MMF dose was adapted **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MPA **Method of measurement**: C_0 **Frequency of MPA measure**: monthly **Assay used**: EMIT 2000	**Health outcome**: renal function creatinine levels trigycerides cholesterol diastolic blood pressure **acute rejection** **Length of followup**: mean 61.5 $\pm$ 6.1m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Pape **Year**: 2004 **Country**: Germany	**Aim**: To determine whether long term monitoring in pediatric renal graft recipients improves quality of immunosuppression **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 42 **Analyzed**: NR	**Population**: Children and adults – min 1y after renal tx **Organ transplanted**: Kidney (Renal) **Age**: Mean for entire population median 9.4y Range 1.4 - 15.1y **% Male**: 64.3 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 600 mg/m2 BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: Predose concentration **Frequency of MPA measure**: every 3 months **Assay used**: LC-MS	**Health outcome**: NR **Length of followup**: 2y
Author: Pawinski **Year**: 2006a **Country**: Poland	**Aim**: To examine the ability of PK to discriminate between patients with and without acute rejection **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 51 **Analyzed**: 51	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 48y Range 17–62y **% Male**: 52.9 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Tacrolimus Prednisone	**Form measured**: MPA MPAG **Method of measurement**: C_0, C_{max}, AUC_{0-12} **Frequency of MPA measure**: at day 7, 6 - 8 weeks and 3 m **Assay used**: HPLC	**Health outcome**: acute rejection **Length of followup**: 3m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Pawinski **Year**: 2006b **Country**: Poland	**Aim**: To investigate the effect of time on PK of MPA in early posttransplant period **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 33 CsA: 23 patients Tac: 10 patients **Analyzed**: 33	**Population**: Adult renal tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Range 17–62y **% Male**: 45.5 **Weight**: Range 40-86 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 0.5 - 2 g/day **Prospective dose adjustment planned**: Yes - based on clinical indicators toxicity **Concomitant medications**: Cyclosporine Tacrolimus Prednisone	**Form measured**: MPA MPAG **Method of measurement**: C_0, AUC_{0-2}, AUC_{0-12} concentration **Frequency of MPA measure**: 1wk, 2m, 3m **Assay used**: HPLC	**Health outcome**: acute rejection leucocyte cell count hemotocrit **Length of followup**: 3m
Author: Pillans **Year**: 2001 **Country**: Australia	**Aim**: Assess the relationship between a single four-point MPA AUC measurement performed in the first week after transplant, as well as median trough cyclosporin concentration before rejection or during the first month and clinical outcomes in the first month. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 27 **Analyzed**: 27	**Population**: Caucasian from single center **Organ transplanted**: Kidney (Renal) **Age**: Range 21-65 y **% Male**: 78 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: C_o AUC_{0-12} (as predicted by LSS C_0, C_1, C_3, C_6) **Frequency of MPA measure**: once (day 3-5) **Assay used**: HPLC	**Health outcome**: Biopsy-proven acute rejection Gastrointestinal adverse events **Length of followup**: 1m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Reggiani **Year**: 2005 **Country**: Italy	**Aim**: To evaluate Tac and MMF with steroids and to evaluate PK of MPA **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: 30 Group A: 12 patients Group B: 18 patients **Analyzed**: 30	**Population**: Liver transplant tx **Organ transplanted**: Liver **Age**: Mean for entire population group A: 49.7 +/- 4.6, group B: 50.4 +/- 8.9 **% Male**: Entire population 70, group A: 66.7, group B: 72.2 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 750 mg BID 1st month, 500 mg BID > 1 month **Prospective dose adjustment planned**: No **Concomitant medications**: Tacrolimus group A and B Methylpred. group B Prednisone group B	**Form measured**: MPA **Method of measurement**: AUC_{0-12} **Frequency of MPA measure**: 1wk and 1m **Assay used**: NR	**Health outcome**: leucopenia, low platelet count, GI and neurological symptoms **Length of followup**: mean 31 +/- 7m
Author: Ringe **Year**: 2001 **Country**: Germany	**Aim**: Pilot study to investigate a novel steroid-free immunosuppressive regimen after clinical liver transplantation **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 30 **Analyzed**: 30	**Population**: NR **Organ transplanted**: LIver **Age**: Median 51.9y Range 15–66y **% Male**: 70 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2315 to 2320 mg/kg/day **Prospective dose adjustment planned**: No **Concomitant medications**: Tacrolimus	**Form measured**: MPA **Method of measurement**: 12 hr post dose **Frequency of MPA measure**: Daily **Assay used**: HPLC	**Health outcome**: acute rejection diarrhea **Length of followup**: 2y

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Satoh **Year**: 2006 **Country**: Japan	**Aim**: To investigate MPA chronopharmacokinetics and relation between MPA circadian exposure and incidence of acute rejection **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 30 **Analyzed**: 30	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 41.2 +/- 2.1y Range 21–66y **% Male**: 50 **Weight**: Mean 56.4 +/-1.9 Range (37.0-81.0)	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day **Prospective dose adjustment planned**: Yes - based on clinical indicators GI symptoms **Concomitant medications**: Tacrolimus Methylpred. Corticosteroids	**Form measured**: MPA **Method of measurement**: C_o C_{max} AUC_{0-12} **Frequency of MPA measure**: 13 samples in 24 hrs, just prior, 1, 2, 3, 6, 9, and 12 hr after each dose (2 doses a day) **Assay used**: HPLC	**Health outcome**: acute rejection diarrhea nausea abdominal pain vomiting **Length of followup**: NR
Author: Satoh **Year**: 2005 **Country**: Japan	**Aim**: To investigate the influence of MMF on incidence of acute rejection and infectious complications **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 66 **Analyzed**: 66	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean for entire population AZA: 37.9 +/- 11.5 MMF: 44.3 +/- 11.6 **% Male**: Entire population AZA: 54.5, MMF: 59.1 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1.0 – 2 g/day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Tacrolimus Methylpred. Prednisone	**Form measured**: MPA **Method of measurement**: $AUC_{(0-12h)}$ **Frequency of MPA measure**: just before dose and 1,2,3,6,9 and 12 h after morning oral administration **Assay used**: HPLC	**Health outcome**: viral infection acute rejection CMV infections Varicella Zoster Malignancy related Epstein-Barr Adenovirus hemorrhagic cystitis **Length of followup**: 28d

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Shaw **Year**: 2000 **Country**: USA	**Aim**: Possibility of an effect of ethnicity on the PK of MPA **Comparison of monitored patients with others**: Yes Two set s of monitored patients: AUC controlled vs MPA C_o **Study design**: Prospective Cohort **Entered into study**: African American: 13 Caucasian: 20 **Analyzed**: NR	**Population**: Adult renal transplant **Organ transplanted**: Kidney (Renal) **Age**: Range 47 +/-9.7y **% Male**: 70 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels AUC level, predose trough level **Concomitant medications**: Neoral Steriods	**Form measured**: MPA MPAG **Method of measurement**: C_o C_{max} AUC_{0-12} (as predicted by LSS of C_o, C_{20}, C_{40}, C_{75}, C_{120}) **Frequency of MPA measure**: day 4,7,14,28,90 **Assay used**: HPLC	**Health outcome**: Rejection, leukopenia, gastrointest-inal toxicity **Length of followup**: 90d
Author: Shaw **Year**: 1997 **Country**: USA	**Aim**: PK of MPA in Renal Transplant patients with delayed graft function **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 8 **Analyzed**: 8	**Population**: recent kidney transplant with delayed graft function having one hemodialysis within previous 24 hr. **Organ transplanted**: Kidney (Renal) **Age**: Range 31–58y **% Male**: 50% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) oral MMF **Dose**: 3 g/day for 28d **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Methylpred. azathioprine	**Form measured**: MPA MPAG fMPA MPA free faction **Method of measurement**: Predose concentration MPA free faction %creatinine linear regression model **Frequency of MPA measure**: predose plus 7 X/d once a wk for 5 wks **Assay used**: HPLC	**Health outcome**: hemodialysis did not lower MPA plasma concentration hemodialysis id remove some MPAG from the blood renal function is the primary determinant of MPAG plasma concentration **Length of followup**: 28d

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Smak Gregoor **Year**: 2000b **Country**: Netherlands	**Aim**: Compare the effect of conversion to either MMF or AZA with predisone **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: Condition 1 MMF - 34 Condition 2 AZA - 30 **Analyzed**: 64	**Population**: Stable kidney recipients on CsA and prednisone 1 year post transplant **Organ transplanted**: Kidney (Renal) **Age**: Mean for entire population MMF - 46; AZA - 44 Range for entire population MMF - 21-73; AZA - 22-67 **% Male**: Entire population MMF - 56, AZA - 60 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID **Prospective dose adjustment planned**: No prescribed plan; only if physician allows **Concomitant medications**: Prednisone	**Form measured**: MPA **Method of measurement**: C_0, C_{12h} **Frequency of MPA measure**: NR **Assay used**: EMIT	**Health outcome**: acute rejection side effects **Length of followup**: MMF: 1.61 +/- 0.6y AZA: 1.72 +/- 0.54y
Author: Smak Gregoor **Year**: 2000a **Country**: Netherlands	**Aim**: Describes the results of dose reduction and MPA trough levels in renal tranplant patients treated with MMF and prednisone **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 27 **Analyzed**: 27	**Population**: Stable 1y post kidney tx **Organ transplanted**: Kidney (Renal) **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID, 750 mg BID, 500 mg BID **Prospective dose adjustment planned**: No **Concomitant medications**: Prednisone	**Form measured**: MPA **Method of measurement**: Trough levels **Frequency of MPA measure**: 4,8,12m **Assay used**: EMIT	**Health outcome**: rejection **Length of followup**: 1y

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Smak Gregoor **Year**: 1998 **Country**: Netherlands	**Aim**: The results of monitoring MPA trough levels in relation to adverse events. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 24 **Analyzed**: 15	**Population**: patients converted from azathioprine cyclosporin and prednisone to MMF, cyclosporin & prednisone 1y after transplant **Organ transplanted**: Kidney (Renal) **Age**: NR **% Male**: NR **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: MPA trough levels **Frequency of MPA measure**: 3 times over 2 wks **Assay used**: EMIT	**Health outcome**: hair loss (alopecia) anemia **Length of followup**: 2w
Author: Sugioka **Year**: 2006 **Country**: Japan	**Aim**: To obtain more useful information for therapeutic drug monitoring of MPA after MMF dosing in Japanese renal transplant patients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: Entire population 83 Condition 1 63 Condition 2 20 **Analyzed**: Condition 1 53 on day 14, 50 on day 28 Condition 2 NR	**Population**: Recent renal tx patients **Organ transplanted**: Kidney (Renal) **Age**: Range for entire population MPA group: 7-69y, PSL group: 11 - 66y **% Male**: Entire population MPA group: 65.1 PSL group: 55 both: 62.7 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: MPA group: 1000 to 1500 mg/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MPA **Method of measurement**: $AUC_{(0\text{-}9h)}$ **Frequency of MPA measure**: day 7, 14, 21, 28 post transplantation **Assay used**: EMIT	**Health outcome**: leukopenia diarrhea **Length of followup**: 28d

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Sumethkul **Year**: 2005 **Country**: Thailand	**Aim**: To assess early MPA delivery by E-MPS **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 12 **Analyzed**: 12	**Population**: NR **Organ transplanted**: Kidney (Renal) **Age**: Mean 39 +/- 9y **% Male**: NR **Weight**: Mean 48.1 +/- 8.8kg	**Form given**: Mycophenolate sodium (Myfortic - enteric coated, EC - delayed release) **Dose**: 720 mg BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA MPAG **Method of measurement**: $AUC_{(0\text{-}12h)}$ **Frequency of MPA measure**: NR **Assay used**: HPLC	**Health outcome**: GI side effects acute allograft dysfunction borderline acute rejection **Length of followup**: 3 - 8m
Author: Takahashi **Year**: 1995 **Country**: Japan	**Aim**: MMF in the prevention of acute rejection following renal transplant. **Comparison of monitored patients with others**: No **Study design**: Non-randomized Controlled Trial **Entered into study**: Condition 1 1000 mg n=12 Condition 2 2000 mg n= 10 Condition 3 3000 mg n=10 **Analyzed**: Condition 1 1000 mg n = 12 Condition 2 2000 mg n= 9 Condition 3 3000 mg n= 10	**Population**: Patients receiving first renal transplant, ≥16y **Organ transplanted**: Kidney (Renal) **Age**: Range: 37.7–41y **% Male**: 68.75% **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) MMF (RS-61443) **Dose**: 1000, 2000, or 3000 mg/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine steroids (no description)	**Form measured**: MPA **Method of measurement**: C_0 $AUC_{0\text{-}12}$ **Frequency of MPA measure**: Trough plasma levels and 12-hour AUC were monitored at weeks 1, 2 & 3. Clicial lab testing including CMV titers was performed on a weekly or biweekly basis. **Assay used**: NR	**Health outcome**: patient survival graft survival pancyto-penia gastrointes-tinal disturban-ces numbness of limbs & tongue hemorrha-gic duodenal ulcer **Length of followup**: 12wks

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Tredger **Year**: 2004 **Country**: UK	**Aim**: To determine a target range of MPA plasma levels that reduced adverse events **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: 147 adults, 63 children **Analyzed**: 147 adults, 63 children	**Population**: Liver allograft recipients **Organ transplanted**: Liver **Age**: Mean for entire population adults median: 50.1y, children median: 3.5y Range for entire population adults: 16.9 - 71.8y, children: 0.3 - 19.5y **% Male**: Entire population adults: 53.1, children: 49.2 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: adults: 500 mg BID then increased, children: 5 mg/kg BID then increased **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels to achieve therapeuic levels and also based on clinical **Concomitant medications**: Cyclosporine Tacrolimus	**Form measured**: MPA **Method of measurement**: trough levels **Frequency of MPA measure**: 3 assays per week **Assay used**: EMIT	**Health outcome**: acute rejection leucopenia infection GI **Length of followup**: 2y

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Tsaroucha **Year**: 2000 **Country**: USA	**Aim**: Determine the therapeutic trough levels of MPA and MPAG in kidney, liver and small bowel transplant patients who received both Tac and MMF, in order to assess potential differences in the bioavailability. i.e., effectiveness of this agent between the three groups **Comparison of monitored patients with others**: No **Study design**: Prospective Cohort **Entered into study**: Condition 1 liver: 83 Condition 2 small bowel: 15 Condition 3 kidney: 25 **Analyzed**: Condition 1 liver: 83 Condition 2 small bowel: 15 Condition 3 kidney: 25	**Population**: liver, small bowel and kidney tx **Organ transplanted**: Kidney (Renal) Liver Small bowel **Age**: Mean for groups: liver: 41.4 +/- 4.6y; small bowel: 18.7 +/- 3.9y; kidney: 44.3 +/- 2.7y **% Male**: liver: 70; small bowel: 40; kidney: 52 **Weight**: Mean liver: 74.2; small bowel: 38.7; kidney:77.1	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: liver: 0.0258 g/kg/day small bowel: 0.0822 g/kg/day kidney: 0.0194 g/kg/day **Prospective dose adjustment planned**: No **Concomitant medications**: Tacrolimus steroids	**Form measured**: MPA MPAG **Method of measurement**: trough **Frequency of MPA measure**: 5 to 30 measures/subject **Assay used**: HPLC	**Health outcome**: rejection **Length of followup**: liver: 165d; small bowel: 58d; kidney: 373d; all post transplant
Author: van Besouw **Year**: 1999 **Country**: Netherlands	**Aim**: Observe the effect of MMF on haematological parameters such as haemoglobin (Hb), leukocytes and thrombocytes **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 26 **Analyzed**: 26	**Population**: Stable renal tx patients without rejection at 12m post tx **Organ transplanted**: Kidney (Renal) **Age**: NR **% Male**: 46 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day – 1 g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Prednisone	**Form measured**: MPA **Method of measurement**: trough **Frequency of MPA measure**: 4m to 8m on MPA 16m to 20m post tx **Assay used**: EMIT	**Health outcome**: leukocytes decrease in Hb **Length of followup**: 8m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: van Gelder **Year**: 1999 **Country**: Netherlands	**Aim**: Provide a data set consisting of well-distributed MPA area under the curve (AUC) data in a population of kidney transplant recipients, using biopsy-proven rejection over a 6-month period after transplantation as the end point **Comparison of monitored patients with others**: Three target MPA AUC values compared **Study design**: RCT **Entered into study**: 154 **Analyzed**: 150	**Population**: Adult recipients of a primary or secondary cadaveric kidney transplant; Caucasian L: 94.1%, I: 91.5%, H: 94.2% **Organ transplanted**: Kidney (Renal) **Age**: Range L: 47.8 +/- 11.5; I: 46.9 +/- 13.8; H: 50.6 +/- 10.5 **% Male**: L: 58.8; I: 63.8; H: 59.6 **Weight**: Range L: 69.8 +/- 12.5 kg I: 65.9 +/- 13.1 kg H: 67.4 +/- 11.3 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: L: 16.1 ug hr/ml I: 32.2 ug hr/ml H: 60.6 ug hr/ml **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Prednisone Corticosteroids	**Form measured**: MPA **Method of measurement**: C_o C_{max} AUC_{0-12} **Frequency of MPA measure**: day 3,7,11,21,28 week 8,12,16,20 **Assay used**: HPLC	**Health outcome**: acute rejection adverse events (vomit, abdominal pain, diarrhea leukopenia pneumonia **Length of followup**: 6m
Author: Wang **Year**: 1998 **Country**: China	**Aim**: Compare the efficiency and safety of MMF on the dosage between 2.0 g/day and 1.5 g/day in order to find appropriate doasge of MMF **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: 13 **Analyzed**: 13	**Population**: Primary cadaveric renal tx recipients **Organ transplanted**: Kidney (Renal) **Age**: Range 35-59y **% Male**: 54 **Weight**: Range 35-68 kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: Group 1. 1.0 g BID Group 2. 0.75 g BID **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine Corticosteroids Methylpred. Prednisone	**Form measured**: MPA **Method of measurement**: C_o C_{max} AUC_{0-12} **Frequency of MPA measure**: day 21 **Assay used**: HPLC	**Health outcome**: Mild rejection, adverse effects **Length of followup**: 3m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Wang **Year**: 2007 **Country**: China	**Aim**: Explore the PK characteristics and therapeutic window of MPA in elderly Chinese recipients to establish a practical model equation to estimate MPA AUC in this age group by LSS **Comparison of monitored patients with others**: No **Study design**: Prospective cohort **Entered into study**: Elderly group: 24 Adult group: 24 **Analyzed**: Elderly group: 24 Adult group: 24	**Population**: Chinese patients, elderly group versus adult group **Organ transplanted**: Kidney **Age**: Elderly group: 65.6 ± 3.6y Adult group: 39.6 ± 14.3y **% Male**: Elderly group:: 71 Adult group: 63 **Weight**: Elderly group: 61.4 ± 8.6kg Adult group: 65.9 ± 10.8kg	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: First 2-4w: 0.75 g BID After 2-4w, 0.5 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: C_0, AUC_{0-12} **Frequency of MPA measure**: Once at 10-12w **Assay used**: HPLC	**Health outcome**: Acute rejection Severe adverse events: pneumonia, leukocyte-penia, death **Length of followup**: 6m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Weber **Year**: 2006 **Country**: Germany	**Aim**: To estimate MPA exposure in pediatric renal transplant patients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: Condition 1 : 54 Condition 2 : 25 **Analyzed**: Condition 1: 54 Condition 2: 25	**Population**: German study: 54 pediatric renal transplant patients in the German study group on MMF therapy; 44 had primary transplant function, 10 had delayed graft function suspension trial: 25 pediatric renal transplant recipients in the Tricontinental MMF trial **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement NR (published in previous reports) Range for entire population german study: 3.17-16.0y, suspension trial: 1.0-16.0y **% Male**: Entire population German study: 61.1, suspension trial: 68.0, both: 63.3 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: German study: 600 mg/m2 BSA up to 2 g/day suspension trial: 600 mg/m2 body surface area BID (up to 1000mg BID), corresponding to 1 g MMF BID in adult renal transplant recipients **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine CsA microemulsion: German study and suspension trial Methylpred. German study Prednisone suspension trial corticosteroids	**Form measured**: MPA German study and suspension trial MPAG suspension trial **Method of measurement**: suspension trial **Frequency of MPA measure**: german study: day 7 and 21 post transplant (initial phase) and 3 and 6m post transplant (stable phase) suspension trial: day 7 and month 3, 9, 24, and 36 **Assay used**: HPLC German study EMIT German study LC-MS suspension trial	**Health outcome**: acute rejection side effects such as leukopenia and infections **Length of followup**: German study: 6m post transplant suspension trial: 36m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Weber **Year**: 2002 **Country**: Germany	**Aim**: To determine the utility of the EMIT assay compared to the HPLC in identifying pediatric renal transplant patients at risk for acute graft rejection. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 50 **Analyzed**: 50	**Population**: all Caucasian **Organ transplanted**: Kidney (Renal) **Age**: Mean 11.8y Range 3.2 - 16.0y **% Male**: 62 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 600 mg/m2 BID to a maximum of 2 g/day **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine Methylpred.	**Form measured**: MPA **Method of measurement**: C_o C_{max} AUC_{0-12} AUC_{0-2} **Frequency of MPA measure**: on day 7 and 21 posttransplant ('initial phase') and 3 and 6 months post transplant ('stable phase') **Assay used**: HPLC EMIT	**Health outcome**: acute rejection leukopenia diarrhea anemia **Length of followup**: 6m
Author: Weber **Year**: 2001 **Country**: Germany	**Aim**: To determine the PK-pharmodynamic realtionship for MPA in pediatric renal transplant patients. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 54 **Analyzed**: 54	**Population**: All patients were caucasian. **Organ transplanted**: Kidney (Renal) **Age**: Inclusion requirement described in study refid 13563, 13860 Range 2.2 - 17.8y **% Male**: 61.1 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 600 mg/m2 BSA twice a day up to 2 g/day max **Prospective dose adjustment planned**: Yes - based on clinical indicators **Concomitant medications**: Cyclosporine Methylpred.	**Form measured**: MPA **Method of measurement**: Predose concentration 0 - 2 hour Predose concentration time to maximum concentration **Frequency of MPA measure**: 7 and 21 days post transplant (initial phase), 3 and 6 months posttransplant (stable phase) **Assay used**: Not reported described in other studies refid 13860, 13867	**Health outcome**: acute rejection leukopenia infections **Length of followup**: 6m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Weber **Year**: 1999 **Country**: Germany	**Aim**: A sequential investigation of MPA PK in initial and stable phase in pediatric renal transplantat recipients. **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 17 **Analyzed**: 17	**Population**: pediatric renal transplant patients **Organ transplanted**: Kidney (Renal) **Age**: Mean 12.0 +/- 0.8y Range 5.9-15.8y **% Male**: 53 **Weight**: Mean 37.6 +/- 3.3	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 600 mg/m2 BSA BID to max of 2g/day **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Methylpred.	**Form measured**: MPA MPAG fMPA **Method of measurement**: $AUC_{(0-12h)}$ T_{max} C_{max} C_{min} **Frequency of MPA measure**: day 7, 21 = initial phase, 3, 6 months = stable phase **Assay used**: HPLC	**Health outcome**: GFR **Length of followup**: 6m
Author: Weber **Year**: 1998 **Country**: Germany	**Aim**: Evaluation of the PK of MPA in Renal transplant patients. **Comparison of monitored patients with others**: No **Study design**: Case control **Entered into study**: Condition 1 children n=18 Condition 2 adults n=10 **Analyzed**: Condition 1 children n=18 Condition 2 adults n=10	**Population**: patients receiving first or second renal transplant **Organ transplanted**: Kidney (Renal) **Age**: Mean children 10.7 +/- 0.72; adults 45.9 +/- 4.1 Range for entire population children 5.9 - 15.3; adults 20.1 - 59.2 **% Male**: 64% (adults and children) **Weight**: Mean children: weight 29.3 +/- 2.49 kg; BSA 1.02 +/- 0.06 m (squared). adults: weight 78.7 +/- 3.2 kg; BSA 1.93 +/- 0.04 m (squared) Range: Children 16-50.3; adults 65.8-98.4	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: Children: 600 mg/m2 body surface area BID Adults: 1 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine cyclosporin A Methylpred.	**Form measured**: MPA MPAG free MPA **Method of measurement**: mimimum concentration MPA-$AUC_{(0-12h)}$ **Frequency of MPA measure**: day 7 and day 21 **Assay used**: HPLC reverse phase	**Health outcome**: transplant dysfunction decreased albumin levels GFR in children creatinine clearance rate in adults **Length of followup**: 3w

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Wolfe **Year**: 1995 **Country**: USA	**Aim**: PK of MMF and IV Ganciclovir alone and in combination in Renal transplant recipients **Comparison of monitored patients with others**: No **Study design**: RCT **Entered into study**: 12 **Analyzed**: 12	**Population**: recent kidney transplant with stable renal functions **Organ transplanted**: Kidney (Renal) **Age**: Mean 36 +/- 13y Range 20-57y **% Male**: 100% **Weight**: Mean 79 +/- 19; lean body weight 69.0 +/- 7.5 Range 56.9-79.9	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: single dose of 1500 mg in each of two treatment arms; one arm alone and one arm combined with ganciclovir **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone Ganciclovir in 2 arms, one arm alone and 1 arm combined with MMF Azathioprine	**Form measured**: MPA MPAG **Method of measurement**: time to peak concentration area under the concentration time curve apparent volume of distributionoral plasma clearancerenal clearance half lifebl **Frequency of MPA measure**: blood: before and 12 times in 48 h after dosing. Urine: 48 hour monitoring **Assay used**: HPLC-UV	**Health outcome**: potential drug interaction between MPA and ganciclovir creatinine clearance **Length of followup**: 3w
Author: Wollenberg **Year**: 1998 **Country**: Germany	**Aim**: to determine PK data of MPA during different periods after transplant. **Comparison of monitored patients with others**: No **Study design**: Non-randomized Controlled Trial **Entered into study**: Condition 1 24 Condition 2 24 **Analyzed**: Condition 1 24 Condition 2 24	**Population**: enrolled after renal transplantation **Organ transplanted**: Kidney (Renal) **Age**: Mean 48 +/- 15y **% Male**: 81 **Weight**: Mean BMI 24.4 +/- 2.4	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1 g BID **Prospective dose adjustment planned**: No **Concomitant medications**: Cyclosporine Prednisone	**Form measured**: MPA **Method of measurement**: trough **Frequency of MPA measure**: after MMF dose: 0.5,1,2,4,6,8 and 12 h **Assay used**: EMIT	**Health outcome**: creatinine **Length of followup**: >3m

Evidence Table 1. General information for all included studies (continued)

Study ID	Study Description	Population	Treatment	Measures	Outcomes
Author: Yamani **Year**: 2000 **Country**: USA	**Aim**: Evaluate the incidence of rejection in relation to MMF trough level following heart transplantation **Comparison of monitored patients with others**: No **Study design**: Retrospective Cohort **Entered into study**: 215 **Analyzed**: 215	**Population**: Heart tx patients **Organ transplanted**: Heart (Cardiac) **Age**: Range 36 +/- 14y **% Male**: 81 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 2 g/day **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Tacrolimus Prednisone	**Form measured**: MPA **Method of measurement**: trough **Frequency of MPA measure**: 12m **Assay used**: EMIT	**Health outcome**: rejection VS trough rejection VS CSA/Tac levels VS MPA levels WBC - lymphocyte (total percent) **Length of followup**: 179 +/- 52d
Author: Zakliczynski **Year**: 2005 **Country**: Poland	**Aim**: To assess clinical utility of MPA trough concentration monitoring in heart transplant patients **Comparison of monitored patients with others**: No **Study design**: Case series **Entered into study**: 76 **Analyzed**: 76	**Population**: Post heart tx patients **Organ transplanted**: Heart (Cardiac) **Age**: Mean 41.9 +/- 16y **% Male**: 75 **Weight**: NR	**Form given**: Mycophenolate mofetil (MMF, CellCept) **Dose**: 1g BID, 1.5 g BID for adjusted >90kg **Prospective dose adjustment planned**: Yes - based on MPA (or metabolite) blood levels **Concomitant medications**: Cyclosporine Tacrolimus Prednisone Azathioprine	**Form measured**: MPA **Method of measurement**: trough levels **Frequency of MPA measure**: NR **Assay used**: EMIT	**Health outcome**: GI symptoms leucopenia anemia **Length of followup**: NR

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Tsaroucha AK, Zucker K, Esquenazi V, et al. Levels of mycophenolic acid and its glucuronide derivative in the plasma of liver, small bowel and kidney transplant patients receiving tacrolimus and cellcept combination therapy. Transpl Immunol 2000;8(2):143-6.

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Wang CX, Meng FH, Chen LZ, et al. Population Pharmacokinetics of Mycophenolic Acid in Senile Chinese Kidney Transplant Recipients. Transplant Proc 2007;39(5):1392-5.

Wang X, Tang X, Xu D. Immunosuppressive effect of mycophenolate mofetil with two different dosages in cadaveric renal transplantation: a short study. Transplant Proc 1998;30(7):3573-4.

Weber LT, Shipkova M, Lamersdorf T, et al. Pharmacokinetics of mycophenolic acid (MPA) and determinants of MPA free fraction in pediatric and adult renal transplant recipients. German Study group on Mycophenolate Mofetil Therapy in Pediatric Renal Transplant Recipients. J Am Soc Nephrol 1998;9(8):1511-20.

Weber LT, Lamersdorf T, Shipkova M, et al. Area under the plasma concentration-time curve for total, but not for free, mycophenolic acid increases in the stable phase after renal transplantation: a longitudinal study in pediatric patients. German Study Group on Mycophenolate Mofetil Therapy in Pediatric Renal Transplant Recipients. Ther Drug Monit 1999;21(5):498-506.

Weber LT, Shipkova M, Armstrong VW, et al. The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic Acid in pediatric renal transplant recipients: a report of the german study group on mycophenolate mofetil therapy. J Am Soc Nephrol 2002;13(3):759-68.

Weber LT, Shipkova M, Armstrong VW, et al. Comparison of the Emit immunoassay with HPLC for therapeutic drug monitoring of mycophenolic acid in pediatric renal-transplant recipients on mycophenolate mofetil therapy. Clin Chem 2002;48(3):517-25.

Weber LT, Hoecker B, Armstrong VW, et al. Validation of an abbreviated pharmacokinetic profile for the estimation of mycophenolic acid exposure in pediatric renal transplant recipients. Ther Drug Monit 2006;28(5):623-31.

Wolfe EJ, Mathur V, Tomlanovich S, et al. Pharmacokinetics of mycophenolate mofetil and intravenous ganciclovir alone and in combination in renal transplant recipients. Pharmacotherapy 1997;17(3):591-8.

Wollenberg K, Krumme B, Schollmeyer P, et al. Pharmacokinetics of mycophenolic acid after renal transplantation. Transplant Proc 1998;30(5):2237-9.

Yamani MH, Starling RC, Goormastic M, et al. The impact of routine mycophenolate mofetil drug monitoring on the treatment of cardiac allograft rejection. Transplantation 2000;69(11):2326-30.

Zakliczynski M, Szewczyk M, Zakliczynska H, et al. Clinical application of monitoring mycophenolic acid trough concentration in heart transplant recipients--single center's experience. Ann Transplant 2005;10(2):38-45.

Appendix D. List of Excluded Studies

CellCept shown to improve 3-year graft survival in renal transplantation. Dialysis & Transplantation 1997;26(8):523
Excluded because not a full report of an included study type

Aigrain EJ, Shaghaghi EK, Baudouin V, et al. Pharmacokinetics of mycophenolate mofetil in eight pediatric renal transplant patients. Transplant Proc 2000;32(2):388-90.
Excluded because MPA levels not associated with any clinical outcomes

Akhlaghi F, Patel CG, Zuniga XP, et al. Pharmacokinetics of mycophenolic acid and metabolites in diabetic kidney transplant recipients. Ther Drug Monit 2006;28(1):95-101.
Excluded because MPA levels not associated with any clinical outcomes

Akoglu B, Wondra K, Caspary WF, et al. Determinants of fasting total serum homocysteine levels in liver transplant recipients. Exp Clin Transplant 2006;4(1):462-6.
Excluded because MPA not measured in blood

Al Aly Z, Sachdeva A, Philoctete Ashley JM, et al. Preliminary experience with mycophenolate mofetil for preservation of renal function in cardiac transplant patients with documented cyclosporine nephrotoxicity. Nephrology 2006;11(2):151-5.
Excluded because not a full report of an included study type

Al Khoury S, Shah N, Afzali B, et al. Post-transplantation anaemia in adult and paediatric renal allograft recipients - Guy's Hospital experience. Nephrol Dial Transplant 2006;21(7):1974-80.
Excluded because MPA not measured in blood

Anil Kumar MS, Moritz MJ, Saaed MI, et al. Avoidance of chronic steroid therapy in African American kidney transplant recipients monitored by surveillance biopsy: 1-year results. Am J Transplant 2005;5(8):1976-85.
Excluded because MPA not measured in blood

Annesley TM, Clayton LT. Quantification of mycophenolic acid and glucuronide metabolite in human serum by HPLC-tandem mass spectrometry. Clin Chem 2005;51(5):872-7.
Excluded because not a full report of an included study type

Arbogast H, Huckelheim H, Schneeberger H, et al. A calcineurin antagonist-free induction/maintenance strategy for immunosuppression in elderly recipients of renal allografts from elderly cadaver donors: long-term results from a prospective single centre trial. Clin Transplant 2005;19(3):309-15.
Excluded because MPA levels not associated with any clinical outcomes

Armstrong VW, Tenderich G, Shipkova M, et al. Pharmacokinetics and bioavailability of mycophenolic acid after intravenous administration and oral administration of mycophenolate mofetil to heart transplant recipients. Ther Drug Monit 2005;27(3):315-21.
Excluded because MPA levels not associated with any clinical outcomes

Arns W, Breuer S, Choudhury S, et al. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. Clin Transplant 2005;19(2):199-206.
Excluded because MPA levels not associated with any clinical outcomes

Arns W, Gies M, Choi L, et al. Absorption characteristics of EC-MPS - An enteric-coated formulation of mycophenolic sodium. Int J Clin Pharmacol Ther 2006;44(8):375-85.
Excluded because MPA levels not associated with any clinical outcomes

Atcheson BA, Taylor PJ, Kirkpatrick CM, et al. Free mycophenolic acid should be monitored in renal transplant recipients with hypoalbuminemia. Ther Drug Monit 2004;26(3):284-6.
Excluded because MPA levels not associated with any clinical outcomes

Au WY, Lie AK, Cheng VCC, et al. Successful Lung Transplantation for Post-BMT Bronchiolitis Obliterans and Lipoid Pneumonia Associated with Atypical Mycobacterium and Aspergillosis Infection. J Heart Lung Transplant 2007;26(8):870-2.
Excluded because not a full report of an included study type

Augustine JJ, Knauss TC, Schulak JA, et al. Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. Am J Transplant 2004;4(12):2001-6.
Excluded because MPA not measured in blood

Aumente R, Arizon Del Prado JM, Lopez Malo De Molina MD, et al. Clinical pharmacokinetics of tacrolimus in heart transplantation: new strategies of monitoring. Transplant Proc 2003;35(5):1988-91.
Excluded because MPA not measured in blood

Aw MM, Brown NW, Itsuka T, et al. Mycophenolic acid pharmacokinetics in pediatric liver transplant recipients. Liver Transplantation 2003;9(4):383-8.
Excluded because MPA levels not associated with any clinical outcomes

Balbontin FG, Kiberd B, Squires J, et al. Tacrolimus monitoring by simplified sparse sampling under the concentration time curve. Transplant Proc 2003;35(7):2445-8.

Excluded because MPA not measured in blood

Baraldo M, Isola M, Feruglio MT, et al. Therapeutic mycophenolic acid monitoring by means of limited sampling strategy in orthotopic heart transplant patients. Transplant Proc 2005;37(5):2240-3.
Excluded because MPA levels not associated with any clinical outcomes

Barcena R, Oton E, Barreales M, et al. Scarce Influence of Corticosteroid Boluses on Long-Term Viral Load and Liver Histology in Transplanted Patients With Recurrent Hepatitis C. Transplant Proc 2006;38(8):2502-4.
Excluded because MPA not measured in blood

Barten MJ, Rahmel A, Chang H, et al. Assessment of immunosuppression by lymphocyte functions in human blood. Transplant Proc 2002;34(7):2876-7.
Excluded because does not report on humans with a solid organ transplant

Barten MJ, Rahmel A, Garbade J, et al. Pharmacodynamic monitoring of the conversion of cyclosporine to tacrolimus in heart and lung transplant recipients. Transplant Proc 2005;37(10):4532-4.
Excluded because MPA levels not associated with any clinical outcomes

Barten MJ, Rahmel A, Garbade J, et al. C0h/C2h monitoring of the pharmacodynamics of cyclosporin plus mycophenolate mofetil in human heart transplant recipients. Transplant
Proc 2005;37(2):1360-1.
Excluded because MPA levels not associated with any clinical outcomes

Barton TD, Blumberg EA, Doyle A, et al. A prospective cross-sectional study of BK virus infection in non-renal solid organ transplant recipients with chronic renal dysfunction. Transplant Infectious Disease 2006;8(2):102-7.
Excluded because MPA not measured in blood

Beaulieu AJ, Lapane KL, Gohh RY, et al. Short-term reproducibility of total homocysteine determinations in stable renal transplant recipients. Transplant Proc 1999;31(5):2121-3.
Excluded because MPA not measured in blood

Beaunoyer M, Busque S, St Louis G, et al. Low-dose tacrolimus, trough-monitored mycophenolate mofetil, and planned steroid withdrawal for cadaveric kidney transplantation: a single center experience. Transplant Proc 2002;34(5):1694-5.
Excluded because MPA levels not associated with any clinical outcomes

Belev B, Simeonov P, Popov R, et al. First observations in our country on the administration of mycophenolate mofetill (cellcept) in patients with translplanted kidney. Nephrolgy, Hemodialysis, Transplantation 1999;5(1):45-6.
Excluded because not published in English

Benech H, Hascoet S, Furlan V, et al. Development and validation of an LC/MS/MS assay for mycophenolic acid in human peripheral blood mononuclear cells. J Chromatogr B: Analyt Technol Biomed Life Sci 2007;853(1-2):168-74.
Excluded because not a full report of an included study type

Berger N, Guggenbichler S, Steurer W, et al. Bloodstream infection following 217 consecutive systemic-enteric drained pancreas transplants. BMC Infect Dis 2006;6:127
Excluded because MPA not measured in blood

Bestetti RB, Souza TR, Lima MF, et al. Effects of a mycophenolate mofetil-based immunosuppressive regimen in Chagas' heart transplant recipients [2]. Transplantation 2007;84(3):441-2.
Excluded because MPA not measured in blood

Bestetti RB, Souza TR, Lima MF, et al. Effects of a mycophenolate mofetil-based immunosuppressive regimen in Chagas' heart transplant recipients. Transplantation 2007;84(3):441-2.
Excluded because not a full report of an included study type

Bogusz MJ, Enazi EA, Hassan H, et al. Simultaneous LC-MS-MS determination of cyclosporine A, tacrolimus, and sirolimus in whole blood as well as mycophenolic acid in plasma using common pretreatment procedure. J Chromatogr B Analyt Technol Biomed Life Sci 2007;850(1-2):471-80.
Excluded because does not report on humans with a solid organ transplant

Bohler T, Nolting J, Kamar N, et al. Validation of immunological biomarkers for the pharmacodynamic monitoring of immunosuppressive drugs in humans. Ther Drug Monit 2007;29(1):77-86.
Excluded because MPA not measured in blood

Boldt A, Barten MJ, Sagner A, et al. The influence of immunosuppressive drugs on T- and B-cell apoptosis via p53-mediated pathway in vitro and in vivo. Transplantation 2006;82(3):422-7.
Excluded because MPA not measured in blood

Borrows R, Chusney G, Loucaidou M, et al. Clinical outcomes of renal transplantation using liquid chromatographic monitoring of tacrolimus. Ther Drug Monit 2006;28(2):269-73.
Excluded because MPA not measured in blood

Borrows R, Chusney G, Loucaidou M, et al. The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil-based renal transplantation. Ther Drug Monit 2007;29(1):122-6.
Excluded because MPA levels not associated with any clinical outcomes

Borrows R, Chusney G, Loucaidou M, et al. Analysis of factors influencing tacrolimus levels and immunoassay bias in renal transplantation. J Clin Pharmacol 2007;47(8):1035-42.
Excluded because MPA not measured in blood

Bravo Soto JA, Esteban De La Rosa RJ, Luna Del Castillo JD, et al. Effect of mycophenolate mofetil regimen on peripheral blood lymphocyte subsets in kidney transplant recipients. Transplant Proc 2003;35(4):1355-9.
Excluded because MPA not measured in blood

Broeders N, Wissing KM, Crusiaux A, et al. Mycophenolate mofetil, together with cyclosporin A, prevents anti-OKT3 antibody response in kidney transplant recipients. J Am Soc Nephrol 1998;9(8):1521-5.
Excluded because MPA not measured in blood

Brown NW, Aw MM, Mieli-Vergani G, et al. Mycophenolic acid and mycophenolic acid glucuronide pharmacokinetics in pediatric liver transplant recipients: effect of cyclosporine and tacrolimus comedication. Ther Drug Monit 2002;24(5):598-606.
Excluded because MPA levels not associated with any clinical outcomes

Brunet M, Oppenheimer F, Martorell J, et al. Mycophenolic acid monitoring: evaluation of the EMIT MPA immunoassay in kidney and lung transplantation. Transplant Proc 1999;31(6):2275-6.
Excluded because MPA levels not associated with any clinical outcomes

Brunet M, Millan O, Jimenez O, et al. New concepts in cyclosporine pharmacokinetic and dynamic monitoring: the impact of concomitant immunosuppression on target C2 concentrations. Transplant Proc 2004;36(2:Suppl):Suppl-441S
Excluded because MPA levels not associated with any clinical outcomes

Brunet M, Crespo M, Millan O, et al. Pharmacokinetics and pharmacodynamics in renal transplant recipients under treatment with cyclosporine and myfortic. Transplant Proc 2007;39(7):2160-2.
Excluded because MPA levels not associated with any clinical outcomes

Buchler M, Lebranchu Y, Beneton M, et al. Higher exposure to mycophenolic acid with sirolimus than with cyclosporine cotreatment. Clin Pharmacol Ther 2005;78(1):34-42.
Excluded because MPA levels not associated with any clinical outcomes

Budde K, Braun KP, Glander P, et al. Pharmacodynamic monitoring of mycophenolate mofetil in stable renal allograft recipients. Transplant Proc 2002;34(5):1748-50.
Excluded because MPA levels not associated with any clinical outcomes

Budde K, Knoll G, Curtis J, et al. Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. Transplant Proc 2005;37(2):912-5.
Excluded because MPA not measured in blood

Budde K, Knoll G, Curtis J, et al. Long-term safety and efficacy after conversion of maintenance renal transplant recipients from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPA, myfortic). Clin Nephrol 2006;66(2):103-11.
Excluded because MPA not measured in blood

Budde K, Glander P, Kramer BK, et al. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant recipients receiving tacrolimus: clinical, pharmacokinetic, and pharmacodynamic outcomes. Transplantation 2007;83(4): 417-24.
Excluded because MPA levels not associated with any clinical outcomes

Budde K, Bauer S, Hambach P. Erratum: Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients (Am J Transplant 7, 4, (888-898) DOI:10.1111/j.1600-6143.2007.01693.x). Am J Transplant 2007;(8):2057
Excluded because not a full report of an included study type

Budde K, Tedesco-Silva H, Pestana JM, et al. Enteric-coated mycophenolate sodium provides higher mycophenolic acid predose levels compared with mycophenolate mofetil: implications for therapeutic drug monitoring. Ther Drug Monit 2007;29(3):381-4.
Excluded because MPA levels not associated with any clinical outcomes

Budde K, Bauer S, Hambach P, et al. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and mycophenolate mofetil in maintenance renal transplant patients. Am J Transplant 2007;7(4):888-98.
Excluded because MPA levels not associated with any clinical outcomes

Bullingham R, Monroe S, Nicholls A, et al. Pharmacokinetics and bioavailability of mycophenolate mofetil in healthy subjects after single-dose oral and intravenous administration. J Clin Pharmacol 1996;36(4):315-24.
Excluded because does not report on humans with a solid organ transplant

Bunnapradist S, Danovitch GM. Minimizing ciclosporin in renal transplant recipients on daclizumab, mycophenolate and steroids. Nature Clinical Practice Nephrology 2007;3(8):426-7.
Excluded because not a full report of an included study type

Butcher JA, Hariharan S, Adams MB, et al. Renal transplantation for end-stage renal disease following bone marrow transplantation: A report of six cases, with and without immunosuppression. Clin Transplant 1999;13(4):330-5.
Excluded because not a full report of an included study type

Calvo N, Sanchez-Fructuoso AI, Conesa J, et al. Renal Transplant Patients With Gastrointestinal Intolerability to Mycophenolate Mofetil: Conversion to Enteric-Coated Mycophenolate Sodium. Transplant Proc 2006;38(8):2396-7.
Excluded because MPA levels not associated with any clinical outcomes

Cantarovich M, Giannetti N, Cecere R. Impact of cyclosporine 2-h level and mycophenolate mofetil dose on clinical outcomes in de novo heart transplant patients receiving anti-thymocyte globulin induction. Clin Transplant 2003;17(2):144-50.
Excluded because MPA not measured in blood

Casas RV, Lopez AV, Rey JLN, et al. Mycophenolic Acid Reaches Therapeutic Levels Whereas Mycophenolate Mofetil Does Not. Transplant Proc 2006;38(8):2400-1.
Excluded because MPA levels not associated with any clinical outcomes

Cattaneo D, Perico N, Gaspari F, et al. Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation. Kidney Int 2002;62(3):1060-7.
Excluded because MPA levels not associated with any clinical outcomes

Cattaneo D, Merlini S, Pellegrino M, et al. Therapeutic drug monitoring of sirolimus: effect of concomitant immunosuppressive therapy and optimization of drug dosing. Am J Transplant 2004;4(8):1345-51.
Excluded because MPA not measured in blood

Cattaneo D, Merlini S, Zenoni S, et al. Influence of co-medication with sirolimus or cyclosporine on mycophenolic acid pharmacokinetics in kidney transplantation. Am J Transplant 2005;5(12):2937-44.
Excluded because MPA levels not associated with any clinical outcomes

Ceglarek U, Casetta B, Lembcke J, et al. Inclusion of MPA and in a rapid multi-drug LC-tandem mass spectrometric method for simultaneous determination of immunosuppressants. Clin Chim Acta 2006;373(1-2):168-71.
Excluded because not a full report of an included study type

Chen H, Peng C, Yu Z, et al. Pharmacokinetics of mycophenolic acid and determination of area under the curve by abbreviated sampling strategy in Chinese liver transplant recipients. Clin Pharmacokinet 2007;46(2):175-85.
Excluded because MPA levels not associated with any clinical outcomes

Chen YH, Zheng KL, Chen LZ, et al. Clinical pharmacokinetics of tacrolimus after the first oral administration in combination with mycophenolate mofetil and prednisone in Chinese renal transplant recipients. Transplant Proc 2005;37(10):4246-50.
Excluded because MPA not measured in blood

Chenhsu RY, Wu YM, Min DI, et al. Effects of mycophenolate mofetil on hematocrit after renal transplantation. Ann Pharmacother 2002;36(9):1479-80.
Excluded because not a full report of an included study type

Cho EK, Han DJ, Kim SC, et al. Pharmacokinetic study of mycophenolic acid in Korean kidney transplant patients. J Clin Pharmacol 2004;44(7):743-50.
Excluded because MPA levels not associated with any clinical outcomes

Cibrik D, Meier-Kriesche HU, Bresnahan B, et al. Renal function with cyclosporine C2 monitoring, enteric-coated mycophenolate sodium and basiliximab: a 12-month randomized trial in renal transplant recipients. Clin Transplant 2007;21(2):192-201.
Excluded because MPA not measured in blood

Cremers S, Schoemaker R, Scholten E, et al. Characterizing the role of enterohepatic recycling in the interactions between mycophenolate mofetil and calcineurin inhibitors in renal transplant patients by pharmacokinetic modelling. Br J Clin Pharmacol 2005;60(3):249-56.
Excluded because MPA levels not associated with any clinical outcomes

Cussonneau X, Bolon-Larger M, Prunet-Spano C, et al. Relationship between MPA free fraction and free MPAG concentrations in heart transplant recipients based on simultaneous HPLC quantification of the target compounds in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2007;852(1-2):674-8.
Excluded because MPA levels not associated with any clinical outcomes

Czock D, Rasche FM, Carius A, et al. Pharmacokinetics and pharmacodynamics of mycophenolic acid after enteric-coated mycophenolate versus mycophenolate mofetil in patients with progressive IgA nephritis. J Clin Pharmacol 2007;47(7):850-9.
Excluded because does not report on humans with a solid organ transplant

Dall'Amico R, Ghiggeri G, Carraro M, et al. Prediction and treatment of recurrent focal segmental glomerulosclerosis after renal transplantation in children. Am J Kidney Dis 1999;34(6):1048-55.
Excluded because MPA not measured in blood

David-Neto E, Pereira Araujo LM, Sumita NM, et al. Mycophenolic acid pharmacokinetics in stable pediatric renal transplantation. Pediatr Nephrol 2003;18(3):266-72.
Excluded because MPA levels not associated with any clinical outcomes

David-Neto E, Pereira LM, Kakehashi E, et al. The need of mycophenolic acid monitoring in long-term renal transplants. Clin Transplant 2005;19(1):19-25.
Excluded because MPA levels not associated with any clinical outcomes

De Geest S, Denhaerynck K, Schafer-Keller P, et al. Supporting medication adherence in renal transplantation - The SMART study. Swiss Medical Weekly 2007;137(SUPPL 155):125S-7S.
Excluded because MPA not measured in blood

Devyatko E, Ploner M, Zuckermann A, et al. Value of mycophenolic acid trough level monitoring after lung transplantation. Transplant Proc 2002;34(5):1881-3.
Excluded because MPA levels not associated with any clinical outcomes

Devyatko E, Zuckermann A, Bohdjalian A, et al. Activation of the purine salvage pathway in mononuclear cells of cardiac recipients treated with mycophenolate mofetil. Transplantation 2006;82(1):113-8.
Excluded because MPA levels not associated with any clinical outcomes

Dharancy S, Hulin A, Declerck N, et al. Mycophenolic acid (MPA) AUC(0-12H) in stable liver transplant patients treated with a monotherapy of mycophenolate mofetil (MMF) for calcineurin inhibitors (CNI) induced nephrotoxicity. Hepatology 2006;44(4, Suppl. 1):406A-7A.
Excluded because not a full report of an included study type

Di Benedetto F, Di Sandro S, De Ruvo N, et al. Sirolimus Monotherapy in Liver Transplantation. Transplantat Proc 2007;39(6):1930-2.
Excluded because MPA not measured in blood

Diekmann F, Campistol JM, Saval N, et al. Sequential quadruple immunosuppression including sirolimus in extended criteria and nonheartbeating donor kidney transplantation. Transplantation 2007;84(3):429-32.
Excluded because not a full report of an included study type

Djebli N, Picard N, Rerolle JP, et al. Influence of the UGT2B7 promoter region and exon 2 polymorphisms and comedications on Acyl-MPAG production in vitro and in adult renal transplant patients. Pharmacogenet Genomics 2007;17(5):321-30.
Excluded because MPA levels not associated with any clinical outcomes

Doria C, Fraser N, Ramirez CB, et al. Use of EC-MPS (MYFORTIC (R), enteric coated mycophenolate sodium) as part of immunosuppression regimen in liver transplant patients suffering from intestinal intolerance and/or poor quality of life related to the use mycophenolate mofetil (MMF). Hepatology 2006;44(4, Suppl. 1):411A-2A.
Excluded because not a full report of an included study type

Dosch AO, Ehlermann P, Koch A, et al. A comparison of measured trough levels and abbreviated AUC estimation by limited sampling strategies for monitoring mycophenolic acid exposure in stable heart transplant patients receiving cyclosporin A-containing and cyclosporin A-free immunosuppressive regimens. Clin Ther 2006;28(6):893-905.
Excluded because MPA levels not associated with any clinical outcomes

Drognitz O, Donauer J, Kamgang J, et al. Living-donor kidney transplantation: The Freiburg experience. Langenbecks Arch Surg 2007;392(1):23-33.
Excluded because MPA not measured in blood

Ducloux D, Motte G, Billerey C, et al. Cyclosporin withdrawal with concomitant conversion from azathioprine to mycophenolate mofetil in renal transplant recipients with chronic allograft nephropathy: a 2-year follow-up. Transpl Int 2002;15(8):387-92.
Excluded because MPA not measured in blood

El Haggan W, Ficheux M, Debruyne D, et al. Pharmacokinetics of mycophenolic acid in kidney transplant patients receiving sirolimus versus cyclosporine. Transplant Proc 2005;37(2):864-6.
Excluded because MPA levels not associated with any clinical outcomes

Engelbertink R, Smak GP, Hesse C, et al. High mycophenolic acid area under-the-curve values in renal transplant recipients on long-term mycophenolate mofetil treatment. Transplant Proc 2002;34(7):2983-4.
Excluded because MPA levels not associated with any clinical outcomes

Ensom MH, Partovi N, Decarie D, et al. Pharmacokinetics and protein binding of mycophenolic acid in stable lung transplant recipients. Ther Drug Monit 2002;24(2):310-4.
Excluded because MPA levels not associated with any clinical outcomes

Ensom MH, Partovi N, Decarie D, et al. Mycophenolate pharmacokinetics in early period following lung or heart transplantation. Ann Pharmacother 2003;37(12):1761-7.
Excluded because MPA levels not associated with any clinical outcomes

Esmatjes E, Flores L, Vidal M, et al. Hypoglycaemia after pancreas transplantation: Usefulness of a continuous glucose monitoring system. Clin Transplant 2003;17(6):534-8.
Excluded because MPA not measured in blood

Ettenger R, Bartosh S, Choi L, et al. Pharmacokinetics of enteric-coated mycophenolate sodium in stable pediatric renal transplant recipients. Pediatr Transplant 2005;9(6):780-7.
Excluded because MPA levels not associated with any clinical outcomes

Fatela-Cantillo D, Hinojosa-Perez R, Peralvo-Rodriguez MI, et al. Pharmacokinetic Evaluation of Mycophenolic Acid Profiles During the Period Immediately Following an Orthotopic Liver Transplant. Transplant Proc 2006;38(8):2482-5.
Excluded because MPA levels not associated with any clinical outcomes

Fernandez A, Martins J, Villlafruela JJ, et al. Variability of mycophenolate mofetil trough levels in stable kidney transplant patients. Transplant Proc 2007;39(7):2185-6.
Excluded because MPA levels not associated with any clinical outcomes

Fernandez A, Marcen R, Pascual J, et al. Mycophenolate mofetil levels in stable kidney transplant recipients. Transplant Proc 2007;39(7):2182-4.
Excluded because MPA levels not associated with any clinical outcomes

Ferraris JR, Ghezzi L, Waisman G, et al. Potential cardiovascular risk factors in paediatric renal transplant recipients. Pediatr Nephrol 2006;21(1):119-25.
Excluded because MPA not measured in blood

Figueras J, Prieto M, Bernardos A, et al. Daclizumab induction and maintenance steroid-free immunosuppression with mycophenolate mofetil and tacrolimus to prevent acute rejection of hepatic allografts. Transpl Int 2006;19(8):641-8.
Excluded because MPA not measured in blood

Filler G, Zimmering M, Mai I. Pharmacokinetics of mycophenolate mofetil are influenced by concomitant immunosuppression. Pediatr Nephrol 2000;14(2):100-4.
Excluded because MPA levels not associated with any clinical outcomes

Filler G, Lepage N, Delisle B, et al. Effect of cyclosporine on mycophenolic acid area under the concentration-time curve in pediatric kidney transplant recipients. Ther Drug Monit 2001;23(5):514-9.
Excluded because MPA levels not associated with any clinical outcomes

Filler G, Feber J. The transplanted child: New immunosuppressive agents and the need for pharmacokinetic monitoring. Paediatrics and Child Health 2002;7(8):525-32.
Excluded because MPA levels not associated with any clinical outcomes

Filler G, Feber J, Lepage N, et al. Universal approach to pharmacokinetic monitoring of immunosuppressive agents in children. Pediatr Transplant 2002;6(5):411-8.
Excluded because MPA levels not associated with any clinical outcomes

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