Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) in press
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article

https://doi.org/10.1631/jzus.B2400069

A practice guideline for therapeutic drug monitoring of mycophenolic acid for solid organ transplants

Shuang LIU[1], Hongsheng CHEN[1], Zaiwei SONG[1], Qi GUO[1], Xianglin ZHANG[2], Bingyi SHI[3], Suodi ZHAI[1], Lingli ZHANG[4], Liyan MIAO[5], Liyan CUI[6], Xiao CHEN[7], Yalin DONG[8], Weihong GE[9], Xiaofei HOU[10], Ling JIANG[11], Long LIU[12], Lihong LIU[2], Maobai LIU[13], Tao LIN[14], Xiaoyang LU[15], Lulin MA[10], Changxi WANG[16], Jianyong WU[17], Wei WANG[18], Zhuo WANG[19], Ting XU[20], Wujun XUE[21], Bikui ZHANG[22], Guanren ZHAO[23], Jun ZHANG[24], Limei ZHAO[25], Qingchun ZHAO[26], Xiaojian ZHANG[27], Yi ZHANG[28], Yu ZHANG[29], Rongsheng ZHAO[1]✉

[1]*Department of Pharmacy, Peking University Third Hospital, Beijing 100191, China*
[2]*Department of Pharmacy, China-Japan Friendship Hospital, Beijing 100029, China*
[3]*Kidney Transplant Quality Control Center of National Health Commission, The 8th Medical Center of Chinese PLA General Hospital, Beijing 100000, China*
[4]*Department of Pharmacy, Sichuan University West China Second University Hospital, Chengdu 610041, China*
[5]*Department of Pharmacy, The First Affiliated Hospital of Soochow University, Suzhou 215006, China*
[6]*Department of Laboratory Medicine, Peking University Third Hospital, Beijing 100191, China*
[7]*Department of Pharmacy, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China*
[8]*Department of Pharmacy, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China*
[9]*Department of Pharmacy, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing 210008, China*
[10]*Department of Urology, Peking University Third Hospital, Beijing 100191, China*
[11]*Department of Pharmacy, Anhui Provincial Hospital, Hefei 230001, China*
[12]*Department of Urology, General Hospital of Northern Theater Command, Shenyang 110003, China*
[13]*Department of Pharmacy, Fujian Medical University Union Hospital, Fuzhou 350001, China*
[14]*Department of Urology, West China Hospital, Sichuan University, Chengdu 610041, China*
[15]*Department of Pharmacy, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[16]*Organ Transplant Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China*
[17]*Kidney Disease Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[18]*Department of Urology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China*
[19]*Department of Pharmacy, Second Military Medical University First Hospital, Shanghai 200433, China*
[20]*Department of Pharmacy, West China Hospital, Sichuan University, Chengdu 610041, China*
[21]*Department of Kidney Transplantation, Nephropathy Hospital, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China*
[22]*Department of Pharmacy, The Second Xiangya Hospital of Central South University, Changsha 410011, China*
[23]*Department of Pharmacy, The 8th Medical Center of Chinese PLA General Hospital, Beijing 100000, China*
[24]*Department of Clinical Pharmacy, The First Affiliated Hospital of Kunming Medical University, Kunming 650032, China*
[25]*Department of Pharmacy, Shengjing Hospital of China Medical University, Shenyang 110004, China*
[26]*Department of Pharmacy, General Hospital of Northern Theater Command, Shenyang 110003, China*
[27]*Department of Phamacy, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*
[28]*Department of Pharmacy, Tianjin First Central Hospital, Tianjin 300192, China*
[29]*Department of Pharmacy, Huazhong University of Science and Technology Tongji Medical College First Clinical College Union Hospital, Wuhan 430022, China*

✉ Rongsheng ZHAO, zhaorongsheng@bjmu.edu.cn
Rongsheng ZHAO, https://orcid.org/0000-0002-3266-3496
Shuang LIU, https://orcid.org/0000-0002-1590-450X

Received Feb. 8, 2024; Revision accepted July 8, 2024;
Crosschecked xxx. xx, 20xx; Published online xxx. xx, 20xx

© Zhejiang University Press 2024

Unedited

Abstract: Objective: Mycophenolic acid (MPA), the active moiety of both mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), serves as a primary immunosuppressant for maintaining solid organ transplants. Therapeutic drug monitoring (TDM) enhances treatment outcomes through tailored approaches. This study aimed to develop an evidence-based guideline for MPA TDM, facilitating its rational application in clinical settings. Methods: The guideline plan drew from the Institute of Medicine and World Health Organization (WHO) guidelines. Using the Delphi method, clinical questions and outcome indicators were generated. Systematic reviews, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence quality evaluations, expert opinions, and patient values guided evidence-based suggestions for the guideline. External reviews further refined the recommendations. Results: The guideline for the TDM of MPA (IPGRP-2020CN099) consists of four sections and 16 recommendations encompassing target populations, monitoring strategies, dosage regimens, and influencing factors. High-risk populations, timing of TDM, area under the curve (AUC) versus trough concentration, target concentration ranges, monitoring frequency, and analytical methods are addressed. Formulation-specific recommendations, initial dosage regimens, populations with unique considerations, pharmacokinetic-informed dosing, body weight factors, pharmacogenetics, and drug–drug interactions are covered. Conclusions: The evidence-based guideline offers a comprehensive recommendation for solid organ transplant recipients undergoing MPA therapy, promoting standardization of MPA TDM and enhancing treatment efficacy and safety.

Key words: Guideline; Mycophenolic acid; Therapeutic drug monitoring; Grading of Recommendations Assessment, Development, and Evaluation (GRADE); Solid organ transplant

unedited

1 Introduction

Mycophenolic acid (MPA) is a class of immunosuppressants commonly used for maintenance therapy in solid organ transplantation. It includes mainly mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) tablets, which are metabolized into MPA (Leichtman, 2007). MPA exerts its immunosuppressive effects by selectively inhibiting the proliferation of T and B lymphocytes via the inhibition of inosine monophosphate dehydrogenase (IMPDH), blocking the de novo synthesis of purine (Behrend and Braun, 2005; Naffouje et al., 2019). MPA exhibits high protein binding rates (97%–99%) (Bergan et al., 2021) and undergoes enterohepatic recirculation (EHRC), which results in non-linear pharmacokinetic (PK) characteristics in the body (de Winter et al., 2011) (Fig. 1). MPA exposure can increase by 50%–100% in the body post-transplantation, and inter-individual variability in MPA PKs can be significant, reaching up to 10-fold (Shaw et al., 2003). To optimize its use in low-toxicity immunosuppressive regimens, personalized MPA dosage through therapeutic drug monitoring (TDM) has been recommended to completely leverage its immunosuppressive effects (Kuypers et al., 2010; Dreesen et al., 2017; Cusumano et al., 2020; Bergan et al., 2021).

Since dosage adjustments of MPA currently rely solely on clinical experience, and evidence-based guidelines for TDM of MPA remain unavailable, the objective of this study was to develop an evidence-based guideline for TDM of MPA in solid organ transplantation, promoting individual usage in clinical practice and improving the safety and efficacy of MPA.

2 Materials and methods

2.1 Guideline registration

The guideline was established as per rigorous international standards, including the World Health Organization (WHO) guidelines (World Health Organization, 2014) and the Appraisal of Guidelines, Research and Evaluation (AGREE II) evaluation criteria (Brouwers et al., 2010). The Canadian Medical Association's guideline development checklist 2.0 (Schünemann et al., 2014) and the Reporting Items for Practice Guidelines in Health Care (RIGHT) criteria (Chen et al., 2017) were also followed to ensure high quality. The guideline has been registered on the International Practice Guidelines Registration Platform (http://www.guidelines-registry.org), registration number IPGRP-2020CN099.

2.2 Evidence syntheses and grading

The Delphi method was used to formulate the clinical questions and outcome measures that should be included in the guideline (Hsu and Sandford, 2007). A literature search was conducted using standard databases from the inception of the databases to 23rd February, 2023, including PubMed, MEDLINE, Cochrane Library, CNKI, WANFANG database, SinoMed, and clinical trials.gov. In total, 36043 articles were identified and screened (Supplementary Appendix). The development group used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the quality of evidence for each clinical question (Balshem et al., 2011). The GRADE system categorized evidence quality into the following four levels: high, moderate, low, and very low (Table 1).

2.3 The values and preferences of patients

A task force was established to determine the preferences and values of patients based on specific clinical inquiries within the guidelines. A cross-sectional survey was conducted to comprehensively understand the receptiveness of patients toward the TDM of MPA (Liu et al., 2024) After compilation and analysis of the outcomes, the results were presented as feedback to the consensus expert panel and the guidance committee members to formulate the recommended guidance.

2.4 Formulation of recommendations

The consensus-forming process was facilitated using the GRADE approach (Table 1) (Balshem et al., 2011). In cases where certain clinical inquiries lacked substantiating evidence, recommendations were created through the synergy of expert clinical knowledge, resulting in consensus-derived guidance referred to as Good Practice Statements (GPS) (Guyatt et al., 2016; Dewidar et al., 2023).

2.5 External review

Once draft recommendations were formulated, they were circulated for external review to frontline healthcare professionals, including a group of 50 clinicians, nurses, and clinical pharmacists. Two patients or their family representatives were also included in the external review process.

unedited

3 Results

The guideline is divided into four sections (Fig. 2), containing a total of 16 recommendations. The detailed literature on the recommendations is listed in the Supplementary Appendix.

3.1 Target population

3.1.1 Question 1: What are the indications for the TDM of MPA?

Recommendation 1: TDM is recommended for populations with the following high-risk factors: modifications in immunosuppressive treatment regimens (dual immunosuppression, reduced calcineurin inhibitor [CNI] dosage, switching between CNI and non-CNI drugs, steroid tapering); concomitant drug interactions; high immunological risk in transplant recipients (early post-transplantation, high rejection risk, secondary transplantation, human leukocyte antigen [HLA] mismatch, and highly sensitized recipients); delayed recovery of transplant organ function; poor medication adherence; gastrointestinal or renal dysfunction; extreme weight; and suspected adverse reactions associated with MPA. **(1C, Strong, Low)**

Evidence summary: The systematic review included 10 studies of high quality (Le Meur et al., 2007; van Gelder et al., 2008; Gaston et al., 2009; Kamar et al., 2009; Le Meur et al., 2011; Li et al., 2013; Fu et al., 2014; Yang et al., 2014; Saliba et al., 2016; Denewar et al., 2021). Quantitative analysis revealed that routine TDM of MPA is associated with a reduced incidence of acute rejection (AR) (relative risk [RR] = 0.63, 95% confidence

interval [CI] [0.41–0.96], P = 0.03), infection (RR = 0.52, 95% CI [0.33–0.81], P = 0.004), and gastrointestinal adverse reactions (RR = 0.50, 95% CI [0.29–0.86], P = 0.01).

Values and preferences: In total, 82.86% of kidney transplant recipients showed a favorable attitude toward the TDM of MPA.

3.2 Monitoring strategies, target concentration ranges, and analytical methods

3.2.1 Question 2: What is the importance of using MPA trough concentration C_0 as a monitoring indicator?

3.2.2 Question 3: What is the importance of the area under the curve (AUC) of MPA as a monitoring indicator?

Recommendation 2: Considering the indicative significance of clinical outcomes, the correlation between C_0 and AUC was poor, with AUC being more indicative. In situations where restricted conditions make AUC measurement infeasible, C_0 can be considered as an alternative. **(2B, Weak, Moderate)**

Evidence summary: The systematic review included only 3 high-quality studies (Dösch et al., 2006; Miura et al., 2011; Todorova et al., 2015), but there was sufficient direct comparative evidence. Qualitative analysis of the studies indicated that the correlation between C_0 and AUC was suboptimal. The morning C_0 of MPA fails to accurately capture overall exposure to the drug, whereas AUC assessment stands as the most effective tool for TDM of MPA. When feasible, AUC is the recommended monitoring indicator to prevent potential misinterpretation from C_0. Consequently, the selection of monitoring indicators should be determined from a thorough analysis of the strengths and limitations of C_0 and AUC, while considering both available monitoring conditions and patient preferences.

3.2.3 Question 4: When is the MPA plasma concentration first measured?

3.2.4 Question 5: What is the AUC sampling time point and calculation method?

Recommendation 3: While monitoring C_0, steady-state trough concentrations should be monitored based on regular administration of MPA every 12 h. **(GPS)**

Recommendation 4: When monitoring AUC, a validated limited sampling strategy (LSS) should be adopted, considering the type of solid organ transplantation and the formulation of the medication. **(1B, Strong, Moderate)**

Evidence summary: Specifically, the average elimination half-life of MPA ranges from 9 to 17 h, influenced by factors such as enterohepatic circulation (Holt, 2002; Ettenger et al., 2005; Arns et al., 2005). Furthermore, steady-state plasma MPA concentrations are typically achieved after a treatment duration of 7 days (Behrend, 2001). A systematic review was performed including 16 studies (van Hest et al., 2004; Ting et al., 2006; Yu et al., 2007; Zhou et al., 2007; de Winter et al., 2009; Musuamba et al., 2009; Pawinski et al., 2009; Capone et al., 2011; Sánchez Fructuoso et al., 2012; Musuamba et al., 2013; Pawinski et al., 2013; Yao et al., 2015; Jia et al., 2017; Zhang et al., 2018; Tanaka et al., 2019; Xiang et al., 2021) with both model development and validation populations of patients. Based on the EHRC of MPA, sampling points for LSS should include samples taken at least 6 h post-administration. Based on the literature, 2 to 4 sampling points were most commonly used for LSS. The most commonly used sampling point for MMF is C_2. The second peak concentration occurs 6–12 h post-administration due to EHRC, and the most commonly used sampling point for this peak is C_8. For EC-MPS, the first peak concentration is found 1.5–2.75 h post-administration, and the most commonly used sampling points are C_1 and C_2. The sampling points for the second peak, which occurs 6–12 h after administration, are C_6, C_8, and C_9. Including these LSS formulas in clinical practice is recommended after further validation and assessment in independent patient populations.

3.2.5 Question 6: What is the therapeutic range of MPA monitoring indicators?

Recommendations 5: The recommended C_0 monitoring ranges for MPA in different solid organ transplantation types are as follows (Table 2).

Recommendation 6: The recommended AUC monitoring ranges for MPA in different solid organ transplantation types are as follows (Table 3).

unedited

Evidence summary: This systematic review included 8 studies (van Gelder et al., 1999; Yamani et al., 2000; van Gelder et al., 2008; Kuypers et al., 2008; Jiang et al., 2015; Liu et al., 2016; Jung et al., 2020; Yabuki et al., 2020), including 2 randomized controlled trials (RCTs) and 6 cohort studies. Qualitative analysis indicated that in renal transplant recipients, an MPA AUC greater than 60 mg·h/L significantly increased the incidence of leukopenia and anemia, whereas an MPA AUC less than 30 mg·h/L significantly increased the incidence of biopsy-proven acute rejection (BPAR). An MPA AUC of 30–60 mg·h/L significantly decreased the incidence of herpes zoster infection. Further restricting the MPA AUC to 22.73–40.46 mg·h/L in lung transplant recipients may offer efficacy and safety benefits by significantly decreasing the cumulative incidence of adverse events, such as infection and chronic transplant lung dysfunction. In renal transplant recipients, an MPA C_0 of less than 3.5 mg/L can significantly decrease the risk of leukopenia and anemia, whereas an MPA C_0 above 2 mg/L in heart transplant recipients can significantly decrease the incidence of rejection. Consistent with the present consensus (Kuypers et al., 2010; Bergan et al., 2021), there is currently insufficient data to support an evidence-based MPA C_0 target in lung transplant recipients.

3.2.6 Question 7: What should be the frequency of MPA blood level monitoring?

Recommendation 7: Generally, it is recommended to monitor MPA concentrations once a week during the first month after transplantation, once a month during the first three months, and once every three months during the first year. After the first year, if the dose is stable, monitoring can be performed while adjusting, adding, or discontinuing drugs that may potentially interact with immunosuppressive agents. Furthermore, immediate monitoring should be performed if there are significant changes to the immunosuppressive regimen, such as CNI dose reduction, discontinuation, or conversion to another CNI or sirolimus, or when rejection, infection, hematological toxicity, malignant tumors, or refractory diarrhea occur. **(GPS)**

Evidence summary: Frequent monitoring is important in the early stages of post-transplantation. Ideally, monitoring should be performed once within the first week, weekly within the first month, monthly within the first three months, and every six months thereafter. Determining the optimal MMF dosage by monitoring the MPA AUC within the first week can decrease variability between patients. A second measurement after 1 or 2 months can account for increasing MPA exposure. Further monitoring is unnecessary unless there are significant changes in the condition or concurrent medication of the patients. After every dosage adjustment or modification involving MPA in the immunosuppressive regimen, it is essential to ensure that MPA reaches a steady-state concentration before further monitoring is conducted.

Values and preferences: Of the renal transplant recipients surveyed, 37.14% agreed to monthly monitoring, 17.14% preferred bi-monthly monitoring, 14.29% chose to monitor every three months, and 31.43% believed monitoring should be performed only when clinically necessary.

3.2.7 Question 8: What method should be used to implement the TDM of MPA?

Recommendation 8: In consideration of the specificity and accuracy of drug monitoring, liquid chromatography-associated analytical methods, such as liquid chromatography-tandem mass spectrometry (LC–MS/MS) and high-performance liquid chromatography (HPLC) can be used for TDM. When conditions are limiting or rapid testing is needed, immunoassays such as enzyme multiplied immunoassay technique (EMIT), particle-enhanced turbidimetric inhibition immunoassay (PETINIA) or cloned enzyme donor immunoassay (CEDIA) can also be performed for TDM. **(1B, Strong, Moderate)**

Evidence summary: The systematic review included 15 studies (Beal et al., 1998; Vogl et al., 1999; Yeung et al., 1999; Hosotsubo et al., 2001; Prémaud et al., 2004; Westley et al., 2005; Westley et al., 2006; Blanchet et al., 2008; Brown et al., 2010; Shipkova et al., 2010; Dasgupta and Johnson, 2013; Kunicki et al., 2015; Lian et al., 2017; Kikuchi et al., 2018; Liu et al., 2020). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (Whiting et al., 2011) was used to evaluate the consistency of the diagnostic accuracy research. Chromatography and immunoassay exhibited good consistency in detecting MPA, and both methods showed good accuracy and precision. However, due to cross-reactivity with MPA metabolites, the immunoassay measured higher MPA concentrations than chromatography, and the mean bias decreased as MPA concentration increased, with liver transplant exhibiting the largest positive bias. For renal transplant recipients undergoing

unedited

TDM using the EMIT method, the target value of AUC should be appropriately increased. Liquid chromatography–mass spectrometry (LC–MS), which has high specificity, requires a small sample volume, provides fast detection, and is considered the gold standard. Unless otherwise indicated, our recommendations will refer to concentrations and AUC obtained by HPLC or LC-MS.

3.3 Dosage regimen

3.3.1 Question 9: Which formulation is preferred, MMF or EC-MPS?

Recommendation 9: MMF and EC-MPS can be used for post-transplantation immunosuppressive therapy. EC-MPS may offer better clinical outcomes for kidney and liver transplant recipients, but caution should be taken in interpreting its gastrointestinal safety. MMF and EC-MPS exhibit similar efficacy and safety profiles in heart transplants. **(2C, Weak, Low)**

Evidence summary: A systematic review was performed, which included 12 studies (Budde et al., 2004; Salvadori et al., 2004; Kobashigawa et al., 2006; Cattaneo et al., 2007; Cooper et al., 2009; Ciancio et al., 2011; Langone et al., 2011; Lopez-Solis et al., 2014; Zhang et al., 2014; Feng et al., 2015; Wang et al., 2015; Zeng et al., 2018). Seven of these studies compared the incidence of rejection in renal transplant recipients using MMF at a dose of 1000 mg twice daily versus EC-MPS at a dose of 720 mg twice daily. Two RCTs compared the incidence of serious infections in renal transplant recipients using MMF versus EC-MPS. The meta-analysis results indicated that EC-MPS decreased the risk of serious infections compared with MMF (RR = 0.64, 95% CI [0.42-0.96], P = 0.03). No significant differences were found between the two groups in other efficacy and safety outcomes.

3.3.2 Question 10: What is the recommended initial dose for MMF?

Recommendation 10: The early use of high-dose MMF after kidney transplantation, based on foreign population data, can decrease the risk of BPAR in adult kidney transplant recipients. However, caution should be taken regarding the risk of leukopenia. During the post-transplantation stable period, low-dose therapy is preferred for tolerability but monitoring for the risk of BPAR is also crucial. However, there is currently a lack of research data on Chinese populations. **(1B, Strong, Moderate)**

Evidence summary: The systematic review included 9 studies (Pichlmayr, 1995; Keown et al., 1996; Neylan, 1997; Mendez, 1998; Squifflet et al., 2001; Flechner et al., 2005; Kocak et al., 2005; Khosroshahi et al., 2009; Gourishankar et al., 2010), of which 6 were RCTs and 3 were cohort studies. Four RCTs compared the effectiveness and safety of high-dose versus standard-dose immunosuppression in 1,128 adult renal transplant recipients. Meta-analysis results indicated that the incidence of BPAR confirmed by biopsy in the high-dose group (1.5 g bid or 1.5 g bid for 1–5 days postoperatively, followed by 1 g bid) was significantly lower than that in the control group (RR = 0.72, 95% CI [0.53–0.99], P = 0.04). The incidence of leukopenia in the high-dose group was significantly higher than that in the control group (RR = 1.41, 95% CI [1.06–1.87], P = 0.02), but the stability of the results was moderate. In total, 5 studies compared the effectiveness and safety of low-dose versus standard-dose immunosuppression in 755 adult renal transplant recipients, including 2 RCTs and 3 cohort studies. Meta-analysis results indicated that the incidence of BPAR confirmed by biopsy in the low-dose group (1g/d or 1–1.5g/d) was significantly higher than that in the control group (RR = 2.94, 95% CI [1.51–5.73], P=0.001).

3.3.3 Question 11: What is the recommended initial dose for EC-MPS?

Recommendation 11: Early use of high-dose EC-MPS after kidney transplantation can decrease the risk of BPAR and infection in adult kidney transplant recipients. Limited evidence supports the use of low-dose regimens and no recommendation has been established. **(1B, Strong, Moderate)**

Evidence summary: This is a summary of a systematic review that included 5 studies (Glander et al., 2010; Sommerer et al., 2011; Ding et al., 2014; Zhang et al., 2016; Peng et al., 2018), 3 of which were RCTs and 2 were cohort studies. Of note, 4 studies compared high-dose immunosuppressant therapy to standard-dose therapy in 509 renal transplant recipients. The meta-analysis showed that the high-dose group exhibited significantly lower rates of BPAR (RR = 0.19, 95% CI [0.04–0.81], P=0.03) and infection (RR = 0.82, 95% CI

unedited

[0.69–0.98], P=0.03). No statistically significant differences were found in other outcomes between the two groups. In total, 1 RCT included 60 renal transplant recipients, which showed no significant differences in efficacy or safety between low-dose and standard-dose EC-MPS.

3.3.4 Question 12: What is the clinical benefit of dosing based on body weight?

Recommendation 12: Body weight should be one of the factors considered when refining dosing regimens, especially in populations with low body weight (body mass index, BMI < 18.5 kg/m^2) or obesity (BMI > 30 kg/m^2). (**1C, Strong, Low**)

Evidence summary: The systematic review included 2 high-quality studies (Kaplan et al., 2010; Yamada et al., 2016). Qualitative analysis indicated that as body weight increased, the clearance rate of MPA increased and AUC decreased with a constant dose of MPA. A dose of 10–16 mg/kg of MMF can achieve an MPA AUC of 30–60 mg·h/L with a 75% probability. Fixed MMF dosing based on body weight alone may not attain optimal MPA concentration exposure in renal transplant recipients weighing less than 50 kg or more than 100 kg. In adult renal transplant recipients with extreme body weights, dose adjustments based on specific clinical characteristics and concentration monitoring may be required.

3.3.5 Question 13: Should PK characteristics be considered in renal transplant recipients with specific physiological conditions?

Recommendation 13: Individualized dosing adjustments should be made based on the PK characteristics of children and the elderly, considering their clinical status and TDM results. Personalization of MMF dosing is recommended, particularly in kidney transplant recipients with significantly impaired renal function, based on the TDM of MPA results (Table 4).

Evidence summary: The systematic review included 8 high-quality studies (González-Roncero et al., 2005, 2007; Mohammadpur et al., 2008; van Gelder et al., 2011; Tang et al., 2017; Jiao et al., 2018; Kulabusaya et al., 2019; Romano et al., 2019) involving renal transplant recipients. In patients with impaired renal function, significant EHRC leads to high MPA exposure and low clearance rates due to high mycophenolic acid glucuronide (MPAG) to MPA conversion. Dose adjustments in delayed graft function recipients significantly decreased total MPA AUC on the third and tenth days after renal transplantation, and were unnecessary after the fourth week. Higher MMF doses may improve outcomes in early delayed graft function recipients due to a higher risk of AR and lower MPA exposure.

unedited

3.3.6 Question 14: Should MPA dosage be individualized during treatment?

Recommendation 14: Based on TDM results and target therapeutic concentrations, along with PK principles and methods, individualized adjustment of MPA doses can be considered using validated PK models. **(1B, Strong, Moderate)**

Evidence summary: Population PK(PPK) models combined with Bayesian estimation can help in determining MPA initial dose and dose adjustment after TDM. Optimization of MMF therapy for renal transplant recipients requires TDM as none of the 11 population PK models that were evaluated in the systematic review (Zhang et al., 2019) fulfilled the criteria of candidate models. Current PPK models for EC-MPS are limited (Rong et al., 2021), with few studies describing free MPA concentration or MPA metabolites (Kiang and Ensom, 2018). Further research is required to investigate key factors affecting the predictability of MMF models by including potential covariates.

3.4 Pharmacogenetics and drug-drug interactions

3.4.1 Question 15: Is it necessary to evaluate the effect of genetic polymorphisms on the blood concentration of MPA?

Recommendation15: Routine genetic monitoring is not recommended for patients on MPA (**1D, Strong, Very low**)

Evidence summary: The systematic review (Na Takuathung et al., 2021) found no significant association between single nucleotide polymorphisms, including those in IMPDH genes, and MPA clinical efficacy. *SLCO1B3 334 T>G* was significantly associated with adverse outcomes after MMF therapy, with carriers of the

SLCO1B3 gene 334G allele having a lower risk of gastrointestinal adverse reactions. *UGT1A9-275 T>A* carriers exhibited significantly lower C_0, C_{max}, and $AUC_{0–12h}$, with CL/F significantly higher than in wild-type individuals. Gene testing has limited value in guiding individualized MMF therapy, and dose adjustments according to gene testing results are not recommended.

3.4.2 Question 16: Is it necessary to evaluate the effect of co-administration on the blood concentration of MPA?

3.4.3 Question 17: Do co-administered drugs that affect the concentration of MPA require dosage adjustment?

Recommendation 16: The listed medications (Table 5) have an important effect on MPA concentration; therefore, this information should be considered in clinical management. (**1B, Strong, Moderate**)

Evidence summary: The significant effect of these medications on MPA concentration should be considered when managing patients undergoing MPA treatment. The database should be updated and referenced regularly (such as the quarterly update of Micromedex) in clinical practice to include drugs that are contraindicated or have severe interactions with MMF or EC-MPS.

4 Discussion

4.1 Summary of recommendations and implementation

MPA plays a crucial role in immunosuppressive therapy for organ transplantation. The PKs of MPA are considerably influenced by different intrinsic and extrinsic factors (Kidney Disease: Improving Global Outcomes Transplant Work Group, 2009; Nelson et al., 2022). Compared with immunosuppressants, such as cyclosporine and tacrolimus, the present implementation status of the TDM of MPA in China still offers important opportunities for improvement, particularly in increasing the number of monitoring institutions and the cumulative number of monitored cases (Cai et al., 2023; Yin et al., 2023).

The guideline clearly defines the high-risk populations who require the TDM of MPA. It provides guidance on the optimal timing for TDM, a comparative analysis between AUC and trough concentration as monitoring parameters, recommendations on target concentration ranges and monitoring frequency, and a comparison of various analytical methods for measuring MPA. Furthermore, the guideline offers evidence-based recommendations suited to different formulations of MPA, initial dosage regimens, special patient populations, PK-informed dosing, considerations associated with body weight factors, pharmacogenetic aspects, and potential drug–drug interactions.

unedited

4.2 Comparison with the existing consensus

In contrast to the preceding two consensuses (Kuypers et al., 2010; Bergan et al., 2021), the present guideline provides an evidence-based supplementary resource. Its primary objective is to improve the application of the TDM of MPA by including higher-quality evidence in the decision-making process. Furthermore, within this guideline, we have used a cross-sectional research design to comprehensively understand and dissect the attitude of patients toward the TDM of MPA and its associated determinants. Impressively, 82.86% of survey respondents demonstrated a willingness, ranging from moderate to strong, to participate in the TDM of MPA. Subgroup analysis indicated that patients who had previously undergone the TDM of MPA exhibited a significantly higher inclination to undergo the procedure again. This emphasizes the tangible support of patients for the practical use of TDM. This significant insight immensely supports the future routine integration of the TDM of MPA into clinical practices.

4.3 Gaps in knowledge

To bridge existing gaps in the literature, forthcoming research initiatives should incorporate population PK studies to characterize various aspects, such as enteric-coated MPA, free MPA concentration, EHRC, and MPA

metabolites (Ferreira et al., 2020). Furthermore, several areas exhibit promising research prospects, such as comparative investigations between the original and generic formulations of MPA within the context of TDM, performing economic evaluations, and considering the unique requirements of special patient populations. The ongoing discussion regarding sampling frequency and the precise definition of therapeutic windows emphasizes the need for further high-quality research efforts to bring clarity to these critical aspects (Chakrabarti et al., 2021; Resztak et al., 2021; Sobiak and Resztak, 2021).

Patients consistently express a strong preference for the TDM of MPA, and their decisions are influenced by factors such as prior experience, understanding of the process, and their level of attentiveness. These insights have substantial value in guiding the development of clinical practice guidelines and optimizing clinical protocols (Bai et al., 2018; Ye et al., 2020).

Presently, a noteworthy gap exists in the availability of patient decision-support tools tailored to the TDM of MPA (Woillard et al., 2021). There is substantial potential for developing decision-support tools that adhere to established quality standards in the future, which can facilitate collaborative medical decision-making between clinicians and patients (Caragata et al., 2016; Sekercioglu et al., 2021). Furthermore, PK/PD modeling and simulation, artificial intelligence, and machine learning methodologies should be considered complementary approaches (Ribba et al., 2020; van Gelder and Vinks, 2021; Zeng et al., 2022).

4.4 Limitations

The investigation of the values and preferences of patients was restricted due to the limited geographic representation and relatively small sample size in the study. Therefore, future studies should include a multicenter patient preference survey, thereby furnishing a broader and more substantiated basis for informing the development of the TDM of MPA guidelines and improving clinical decision-making processes. Further, due to the lack of evidence of the cost-effectiveness of TDM of MPA, its economic effects in different countries were not comprehensively studied.

unedited

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Acknowledgments

This work is supported by the Huatong Guokang Medical Research Fund (2023HT010). We would like to thank External Review Group (including doctors, nurses, clinical pharmacists and patients) for critically revising the draft manuscript.

Wenqian Chen, et al. China-Japan Friendship Hospital, Beijing, China

Wenjing Hou, et al. Beijing Friendship Hospital Affiliated to Capital Medical University, Beijing, China

Kuifen Ma, et al. The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Houwen Lin, et al. Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Han Yan, et al. The Second Xiangya Hospital of Central South University, Changsha, Hunan, China

Chen Shi, et al. Huazhong University of Science and Technology Tongji Medical College First Clinical College Union Hospital, Wuhan, Hubei, China

Pan Chen, et al. The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Weiyi Feng, et al. The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

Feng Qiu, et al. The First Affiliated Hospital of Chongqing Medical University, Chongqing,China

Yanqing Song, et al. The First Bethune Hospital of Jilin University, Changchun, Jilin, China

Author contributions

The following individuals made significant contributions to the development of this practice guideline and the manuscript:

- Rongsheng Zhao and Shuang Liu were responsible for the conception and design of the guideline, as well as the management and organization of the guideline development process.
- Rongsheng Zhao served as the principal investigator for this paper.
- Shuang Liu was responsible for the evidence synthesis and writing the first draft of the manuscript.
- The Evidence Synthesis Team, comprising Hongsheng Chen, Zaiwei Song and Qi Guo, was involved in collecting clinical

questions, literature retrieval, evaluation, synthesis, and grading of evidence, conducting systematic reviews, and formulating the summary of finding tables and the recommendation decision tables.

• The Steering Committee, including Xianglin Zhang, Bingyi Shi, Suodi Zhai, Lingli Zhang and Liyan Miao, made final decisions at each stage of the guideline development and oversaw the entire process.

• The Consensus Panel, consisting of Liyan Cui, Xiao Chen, Yalin Dong, Weihong Ge, Xiaofei Hou, Ling Jiang, Long Liu, Lihong Liu, Maobai Liu, Tao Lin, Xiaoyang Lu, Lulin Ma, Changxi Wang, Jianyong Wu, Wei Wang, Zhuo Wang, Ting Xu, Wujun Xue, Bikui Zhang, Guanren Zhao, Jun Zhang, Limei Zhao, Qingchun Zhao, Xiaojian Zhang, Yi Zhang, Yu Zhang, determined the clinical questions, voted for recommendations, and built consensus.

• All authors contributed to the critical revision and approval of the final manuscript.

Compliance with ethics guidelines

Members of the guideline steering committee, guideline consensus panel, and evidence synthesis team completed a declaration of conflicting interests form before attending guideline meetings. All authors reported no potential conflicts of interest.

Table 1 Grading system for recommendations based on quality of evidence

Category and grade	Definition
Strength of recommendation	
Level 1, strong “We recommend”	Most individuals should receive the recommended course of action
Level 2, weak “We suggest”	Different choices would be appropriate for different patients
Quality of evidence	
High (A)	Further research is very unlikely to change our confidence in the estimate of the effect
Moderate (B)	Further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate
Low (C)	Further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate
Very low (D)	Any estimate of the effect is very uncertain

Table 2 The recommended C_0 ranges

Solid organ transplant	C_0	Strength of recommendation	Certainty of evidence
Renal transplant	<3.5 mg/L	Weak	Low
Heart transplant	>2.0 mg/L	Weak	Low
Liver transplant	1–3.5 mg/L	GPS	
Lung transplant		Lack of high-quality evidence, not yet recommended	

GPS, Good Practice Statements

Table 3 The recommended AUC ranges

Solid organ transplant	AUC	Strength of recommendation	Certainty of evidence
Renal transplant	30-60 mg·h/L	Strong	Low
Heart transplant	>36 mg·h/L	GPS	
Liver transplant	30–60 mg·h/L	GPS	
Lung transplant	22.73–40.46 mg·h/L	Weak	Moderate

AUC, area under the curve; GPS, Good Practice Statements

Table 4 Recommendations for special populations

Special populations	Recommendation	Strength of recommendation	Certainty of evidence
Child	Age under 6 should be taken into consideration as a factor when determining dosage escalation	Weak	Low
Elderly	Elderly individuals should not be routinely considered for dosage adjustment	Weak	Moderate
Pregnancy period	MPA is contraindicated for use in pregnant women and should be avoided for a minimum of six weeks before conception	Strong	Low
Renal dysfunction	The recommendation is to consider it as a factor for	Weak	Moderate

Unedited

	dosage adjustment		
Liver dysfunction	Liver dysfunction should not be routinely considered for dosage adjustment	Weak	Low
Hypoalbuminemia	Lack of high-quality evidence, not yet recommended		
Neutropenia	Neutropenia should be taken into consideration as a factor when determining dosage de-escalation	Weak	Low

Table 5 Management of co-administered drugs of MPA

Drug interactions	**MPA formulation**	**MPA concentration**	**Mechanism**	**Management**
Antacids with Magnesium and Aluminum Hydroxides, Sevelamer, and other calcium-free phosphate binders	MMF, EC-MPS	↓	Absorption↓	At least 2h intervals
Proton pump inhibitors	MMF	↓	Absorption↓	Strengthen drug monitoring
Bile Acid Sequestrates (cholestyramine)	MMF, EC-MPS	↓	Impaired EHRC	Avoid combination
Aminoglycosides, cephalosporin, fluoroquinolones, penicillin, sulfamethoxazole, rifampin metronidazole	MMF, EC-MPS	↓	Impaired EHRC	Strengthen drug monitoring
Cyclosporine	MMF, EC-MPS	↓	Impaired EHRC	Strengthen drug monitoring
Isavuconazole	MMF, EC-MPS	↑	Inhibits glucuronidation	Strengthen drug monitoring
Telmisartan	MMF	↓	Induces glucuronidation	Strengthen drug monitoring
Acyclovir, ganciclovir	MMF, EC-MPS	↑	Coexistence competes for tubular secretion	Strengthen drug monitoring
Probenecid	MMF	↑	Coexistence competes for tubular secretion	Strengthen drug monitoring

MPA, mycophenolic acid; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium; EHRC, enterohepatic recirculation

unedited

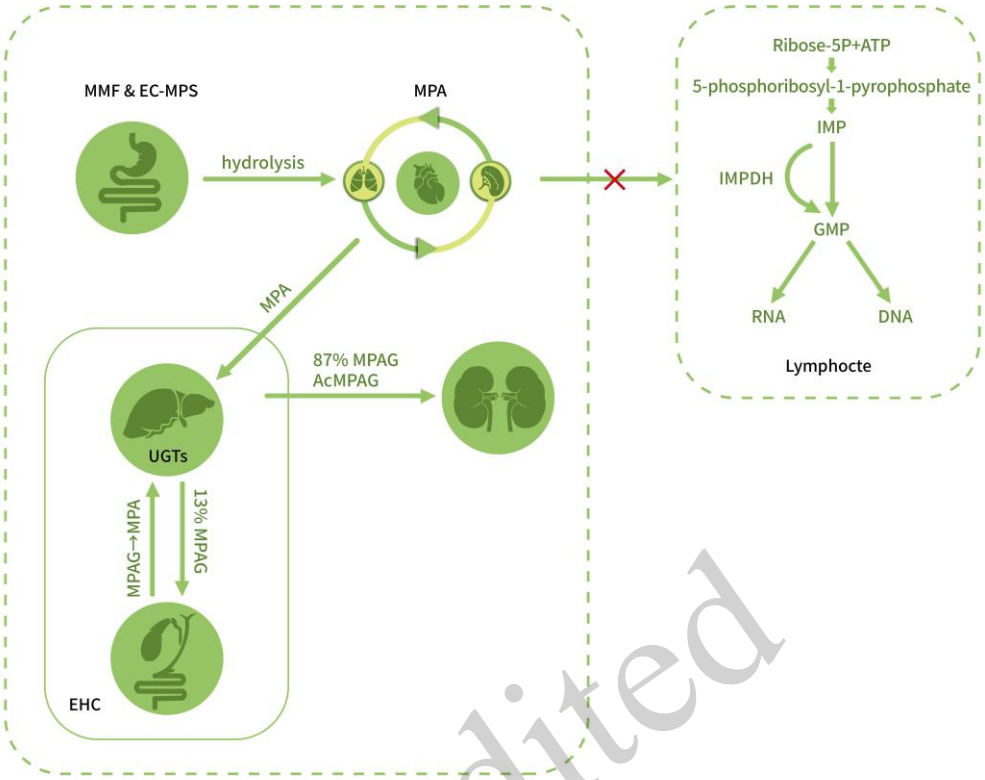

Fig. 1 The pharmacokinetic and pharmacodynamic pathways of MPA

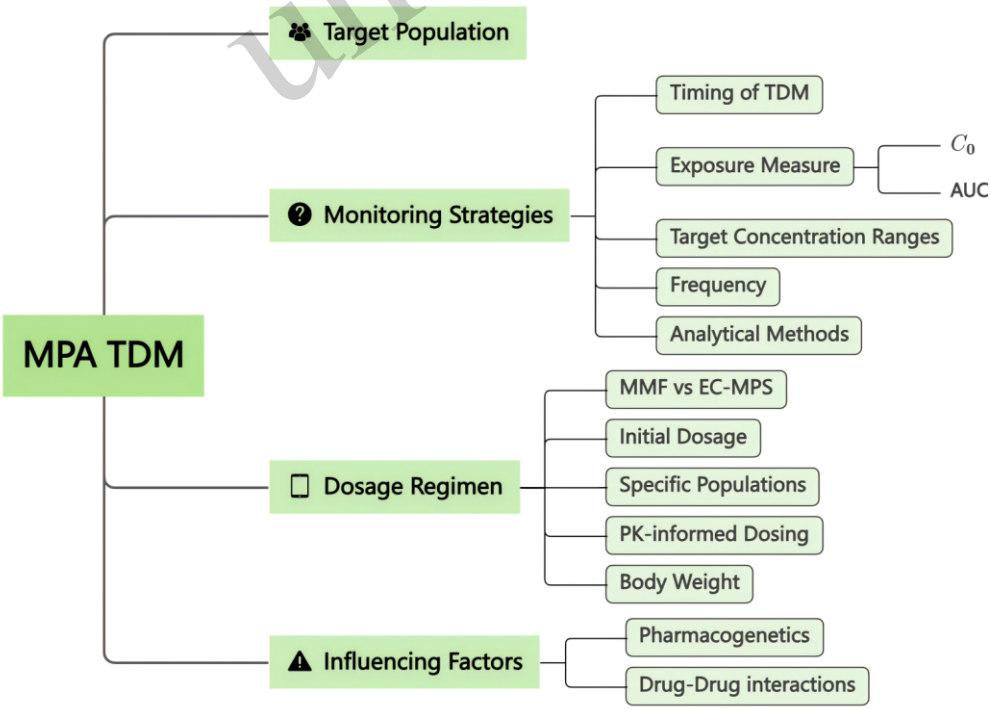

Fig. 2 The framework of the guideline for the TDM of MPA

unedited

References

Arns W, Breuer S, Choudhury S, et al., 2005. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. Clin Transplant, 19(2): 199-206. https://doi.org/10.1111/j.1399-0012.2004.00318.x

Bai F, Ling J, Esoimeme G, et al., 2018. A systematic review of questionnaires about patient's values and preferences in clinical practice guidelines. Patient Prefer Adherence, 12: 2309-2323. https://doi.org/10.2147/PPA.S177540

Balshem H, Helfand M, Schünemann HJ, et al., 2011. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol, 64(4): 401-406. https://doi.org/10.1016/j.jclinepi.2010.07.015

Beal JL, Jones CE, Taylor PJ, et al., 1998. Evaluation of an immunoassay (EMIT) for mycophenolic acid in plasma from renal transplant recipients compared with a high-performance liquid chromatography assay. Ther Drug Monit, 20(6): 685-690. https://doi.org/10.1097/00007691-199812000-00019

Behrend M, 2001. Mycophenolate mofetil: suggested guidelines for use in kidney transplantation. BioDrugs, 15(1): 37-53. https://doi.org/10.2165/00063030-200115010-00004

Behrend M, Braun F, 2005. Enteric-coated mycophenolate sodium: tolerability profile compared with mycophenolate mofetil. Drugs, 65(8): 1037-1050. https://doi.org/10.2165/00003495-200565080-00001

Bergan S, Brunet M, Hesselink DA, et al., 2021. Personalized Therapy for Mycophenolate: Consensus Report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. Ther Drug Monit, 43(2): 150-200. https://doi.org/10.1097/FTD.0000000000000871

Blanchet B, Taieb F, Conti F, et al., 2008. Comparison of a new enzymatic assay with a high-performance liquid chromatography/ultraviolet detection method for therapeutic drug monitoring of mycophenolic acid in adult liver transplant recipients. Liver Transpl, 14(12): 1745-1751. https://doi.org/10.1002/lt.21607

Brouwers MC, Kho ME, Browman GP, et al., 2010. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ, 182(18): E839-E842. https://doi.org/10.1503/cmaj.090449

Brown NW, Franklin ME, Einarsdottir EN, et al., 2010. An investigation into the bias between liquid chromatography-tandem mass spectrometry and an enzyme multiplied immunoassay technique for the measurement of mycophenolic acid. Ther Drug Monit, 32(4): 420-426. https://doi.org/10.1097/FTD.0b013e3181e6b348

Budde K, Curtis J, Knoll G, et al., 2004. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. Am J Transplant, 4(2): 237-243. https://doi.org/10.1046/j.1600-6143.2003.00321.x

Cai M, Zhou L, Gao D, et al., 2023. A national survey of individualized pharmaceutical care practice in Chinese hospitals in 2019. Front Pharmacol, 14: 1022134. https://doi.org/10.3389/fphar.2023.1022134

Capone D, Tarantino G, Kadilli I, et al., 2011. Evalutation of mycophenolic acid systemic exposure by limited sampling strategy in kidney transplant recipients receiving enteric-coated mycophenolate sodium (EC-MPS) and cyclosporine. Nephrol Dial Transplant, 26(9): 3019-3025. https://doi.org/10.1093/ndt/gfq819

Caragata R, Wyssusek KH, Kruger P, 2016. Acute kidney injury following liver transplantation: a systematic review of published predictive models. Anaesth Intensive Care, 44(2): 251-261. https://doi.org/10.1177/0310057X1604400212

Cattaneo D, Cortinovis M, Baldelli S, et al., 2007. Pharmacokinetics of mycophenolate sodium and comparison with the mofetil formulation in stable kidney transplant recipients. Clin J Am Soc Nephrol, 2(6): 1147-1155. https://doi.org/10.2215/CJN.02820707

Chakrabarti K, Frame D, Al Abbas M, et al., 2021. The use of mycophenolate mofetil area under the curve. Curr Opin Rheumatol, 33(3): 221-232. https://doi.org/10.1097/BOR.0000000000000799

Chen Y, Yang K, Marušic A, et al., 2017. A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement. Ann Intern Med, 166(2): 128-132. https://doi.org/10.7326/M16-1565

Ciancio G, Gaynor JJ, Zarak A, et al., 2011. Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplantation with tacrolimus and steroid avoidance: four-year analysis. Transplantation, 91(11): 1198-1205. https://doi.org/10.1097/TP.0b013e3182003d76

Cooper M, Deering KL, Slakey DP, et al., 2009. Comparing outcomes associated with dose manipulations of enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients. Transplantation, 88(4): 514-520. https://doi.org/10.1097/TP.0b013e3181b0e65e

Cusumano JA, Klinker KP, Huttner A, et al., 2020. Towards precision medicine: Therapeutic drug monitoring-guided dosing of vancomycin and β-lactam antibiotics to maximize effectiveness and minimize toxicity. Am J Health Syst Pharm, 77(14): 1104-1112. https://doi.org/10.1093/ajhp/zxaa128

Dasgupta A, Johnson M, 2013. Positive bias in mycophenolic acid concentrations determined by the CEDIA assay compared to HPLC-UV method: is CEDIA assay suitable for therapeutic drug monitoring of mycophenolic acid? J Clin Lab Anal, 27(1): 77-80. https://doi.org/10.1002/jcla.21565

de Winter BC, Mathot RA, Sombogaard F, et al., 2011. Nonlinear relationship between mycophenolate mofetil dose and mycophenolic acid exposure: implications for therapeutic drug monitoring. Clin J Am Soc Nephrol, 6(3): 656-663.

Unedited

https://doi.org/10.2215/CJN.05440610

de Winter BC, van Gelder T, Mathot RA, et al., 2009. Limited sampling strategies drawn within 3 hours postdose poorly predict mycophenolic acid area-under-the-curve after enteric-coated mycophenolate sodium. Ther Drug Monit, 31(5): 585-591. https://doi.org/10.1097/FTD.0b013e3181b8679a

Denewar AA, Mohamed EM, M Ismael MI, et al., 2021. Impact of Therapeutic Dose Monitoring of Mycophenolic Acid on the Outcome of Live-Donor Kidney Transplant Recipients - A Prospective Controlled Study. Saudi J Kidney Dis Transpl, 32(1): 128-136. https://doi.org/10.4103/1319-2442.318514

Dewidar O, Lotfi T, Langendam MW, et al., 2023. Good or best practice statements: proposal for the operationalisation and implementation of GRADE guidance. BMJ Evid Based Med, 28(3): 189-196. https://doi.org/10.1136/bmjebm-2022-111962

Ding C, Xue W, Tian P, et al., 2014. Which is more suitable for kidney transplantation at the early post-transplantation phase in China - low dosing or standard dosing of enteric-coated mycophenolate sodium? Int J Clin Pract Suppl, (181): 10-16. https://doi.org/10.1111/ijcp.12401

Dösch AO, Ehlermann P, Koch A, et al., 2006. 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, 28(6): 893-905. https://doi.org/10.1016/j.clinthera.2006.06.015

Dreesen E, Bossuyt P, Mulleman D, et al., 2017. Practical recommendations for the use of therapeutic drug monitoring of biopharmaceuticals in inflammatory diseases. Clin Pharmacol, 9: 101-111. https://doi.org/10.2147/CPAA.S138414

Ettenger R, Bartosh S, Choi L, et al., 2005. Pharmacokinetics of enteric-coated mycophenolate sodium in stable pediatric renal transplant recipients. Pediatr Transplant, 9(6): 780-787. https://doi.org/10.1111/j.1399-3046.2005.00386.x

Feng JJ, Zhang LW, Zhao P, et al., 2015. Enteric-coated mycophenolate sodium given in combination with tacrolimus has a lower incidence of serious infections in Asian renal-transplant recipients compared with mycophenolate mofetil. Int J Clin Pract Suppl, (183): 1-7. https://doi.org/10.1111/ijcp.12660

Ferreira PCL, Thiesen FV, Pereira AG, et al., 2020. A short overview on mycophenolic acid pharmacology and pharmacokinetics. Clin Transplant, 34(8): e13997. https://doi.org/10.1111/ctr.13997

Flechner SM, Feng J, Mastroianni B, et al., 2005. The effect of 2-gram versus 1-gram concentration controlled mycophenolate mofetil on renal transplant outcomes using sirolimus-based calcineurin inhibitor drug-free immunosuppression. Transplantation, 79(8): 926-934. https://doi.org/10.1097/01.tp.0000155430.52845.51

Fu L, Huang Z, Song T, et al., 2014. Short-term therapeutic drug monitoring of mycophenolic acid reduces infection: a prospective, single-center cohort study in Chinese living-related kidney transplantation. Transpl Infect Dis, 16(5): 760-766. https://doi.org/10.1111/tid.12275

Gaston RS, Kaplan B, Shah T, et al., 2009. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. Am J Transplant, 9(7): 1607-1619. https://doi.org/10.1111/j.1600-6143.2009.02668.x

Glander P, Sommerer C, Arns W, et al., 2010. Pharmacokinetics and pharmacodynamics of intensified versus standard dosing of mycophenolate sodium in renal transplant patients. Clin J Am Soc Nephrol, 5(3): 503-511. https://doi.org/10.2215/CJN.06050809

González-Roncero FM, Gentil MA, Brunet M, et al., 2005. Pharmacokinetics of mycophenolate mofetil in kidney transplant patients with renal insufficiency. Transplant Proc, 37(9): 3749-3751. https://doi.org/10.1016/j.transproceed.2005.09.202

González-Roncero FM, Govantes MA, Chaves VC, et al., 2007. Influence of renal insufficiency on pharmacokinetics of ACYL-glucuronide metabolite of mycophenolic acid in renal transplant patients. Transplant Proc, 39(7): 2176-2178. https://doi.org/10.1016/j.transproceed.2007.06.063

Gourishankar S, Houde I, Keown PA, et al., 2010. The CLEAR study: a 5-day, 3-g loading dose of mycophenolate mofetil versus standard 2-g dosing in renal transplantation. Clin J Am Soc Nephrol, 5(7): 1282-1289. https://doi.org/10.2215/CJN.09091209

Guyatt GH, Alonso-Coello P, Schünemann HJ, et al., 2016. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol, 80: 3-7. https://doi.org/10.1016/j.jclinepi.2016.07.006

Holt DW, 2002. Monitoring mycophenolic acid. Ann Clin Biochem, 39(Pt 3): 173-183. https://doi.org/10.1258/0004563021902035

Hosotsubo H, Takahara S, Imamura R, et al., 2001. Analytic validation of the enzyme multiplied immunoassay technique for the determination of mycophenolic acid in plasma from renal transplant recipients compared with a high-performance liquid chromatographic assay. Ther Drug Monit, 23(6): 669-674. https://doi.org/10.1097/00007691-200112000-00013

Hsu CC, Sandford BA, 2007. The Delphi Technique: Making Sense of Consensus. Pract Assess, Res Eval. 12(10): 1-8. https://doi.org/10.7275/pdz9-th90

Jia Y, Peng B, Li L, et al., 2017. Estimation of Mycophenolic Acid Area Under the Curve With Limited-Sampling Strategy in Chinese Renal Transplant Recipients Receiving Enteric-Coated Mycophenolate Sodium. Ther Drug Monit, 39(1): 29-36. https://doi.org/10.1097/FTD.0000000000000360

Jiang Y, Wang W, Hu X, et al., 2015. Mycophenolate mofetil (MMF) exposure of renal transplantation recipients in stable stage: a

unedited

pharmacokinetic and pharmacodynamic study. Chin J Organ Transplant, 36(4): 217-224. https://doi.org/10.3760/cma.j.issn.0254-1785.2015.04.007

Jiao L Z, DING C G, Tian P X, et al., 2018. Outcomes of EC-MPS combined with low-dose tacrolimus in DCD kidney transplantation for high-risk DGF recipients. Journal of Zhejiang University-Science B (Biomedicine & Biotechnology), 19(06): 481-489. https://doi.org/10.1631/jzus.B1700315

Jung HY, Lee S, Jeon Y, et al., 2020. Mycophenolic Acid Trough Concentration and Dose Are Associated with Hematologic Abnormalities but Not Rejection in Kidney Transplant Recipients. J Korean Med Sci, 35(24): e185. https://doi.org/10.3346/jkms.2020.35.e185

Kamar N, Marquet P, Gandia P, et al., 2009. Mycophenolic acid 12-hour area under the curve in de novo liver transplant patients given mycophenolate mofetil at fixed versus concentration-controlled doses. Ther Drug Monit, 31(4): 451-456. https://doi.org/10.1097/FTD.0b013e3181aa776e

Kaplan B, Gaston RS, Meier-Kriesche HU, et al., 2010. Mycophenolic acid exposure in high- and low-weight renal transplant patients after dosing with mycophenolate mofetil in the Opticept trial. Ther Drug Monit, 32(2): 224-227. https://doi.org/10.1097/FTD.0b013e3181d18baa

Keown P, Hayry P, Morris P,et al., 1996. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation, 61(7): 1029-1037. https://doi.org/10.1097/00007890-199604150-00008

Khosroshahi HT, Shoja MM, Peyrovifar A, et al., 2009. Mycophenolate mofetil dose reduction in renal transplant recipients: a 5-year follow-up study. Transplant Proc, 41(7): 2797-2799. https://doi.org/10.1016/j.transproceed.2009.07.036

Kiang TKL, Ensom MHH, 2018. Population Pharmacokinetics of Mycophenolic Acid: An Update. Clin Pharmacokinet, 57(5): 547-558. https://doi.org/10.1007/s40262-017-0593-6

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group, 2009. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant, 9 Suppl 3: S1 – S155. https://doi.org/10.1111/j.1600-6143.2009.02834.x

Kikuchi M, Tanaka M, Takasaki S, et al., 2018. Comparison of PETINIA and LC-MS/MS for determining plasma mycophenolic acid concentrations in Japanese lung transplant recipients. J Pharm Health Care Sci, 4: 7. https://doi.org/10.1186/s40780-018-0101-7

Kobashigawa JA, Renlund DG, Gerosa G, et al., 2006. Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. J Heart Lung Transplant, 25(8): 935-941. https://doi.org/10.1016/j.healun.2006.04.005

Kocak H, Yakupoglu U, Karatas GU, et al., 2005. Tacrolimus plus low-dose mycophenolate mofetil in renal transplant recipients: better 2-year graft and patient survival than with a higher mycophenolate mofetil dose. Transplant Proc, 37(7): 3009-3011. https://doi.org/10.1016/j.transproceed.2005.07.033

Kulabusaya B, Vadcharavivad S, Avihingsanon Y, et al., 2019. Early pharmacokinetics of low dosage mycophenolate exposure in Thai kidney transplant recipients. Int J Clin Pharm, 41(4): 1047-1055. https://doi.org/10.1007/s11096-019-00848-w

Kunicki PK, Pawiński T, Boczek A, et al., 2015. A Comparison of the Immunochemical Methods, PETINIA and EMIT, With That of HPLC-UV for the Routine Monitoring of Mycophenolic Acid in Heart Transplant Patients. Ther Drug Monit, 37(3): 311-318. https://doi.org/10.1097/FTD.0000000000000151

Kuypers DR, de Jonge H, Naesens M, et al., 2008. Current target ranges of mycophenolic acid exposure and drug-related adverse events: a 5-year, open-label, prospective, clinical follow-up study in renal allograft recipients. Clin Ther, 30(4): 673-683. https://doi.org/10.1016/j.clinthera.2008.04.014

Kuypers DR, Le Meur Y, Cantarovich M, et al., 2010. Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. Clin J Am Soc Nephrol, 5(2): 341-358. https://doi.org/10.2215/CJN.07111009

Langone AJ, Chan L, Bolin P, et al., 2011. Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study. Transplantation, 91(4): 470-478. https://doi.org/10.1097/TP.0b013e318205568c

Le Meur Y, Büchler M, Thierry A, et al., 2007. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant, 7(11): 2496-2503. https://doi.org/10.1111/j.1600-6143.2007.01983.x

Le Meur Y, Thierry A, Glowacki F, et al., 2011. Early steroid withdrawal and optimization of mycophenolic acid exposure in kidney transplant recipients receiving mycophenolate mofetil. Transplantation, 92(11): 1244-1251. https://doi.org/10.1097/TP.0b013e318234e134

Leichtman AB, 2007. Balancing efficacy and toxicity in kidney-transplant immunosuppression. N Engl J Med, 357(25): 2625-2627. https://doi.org/10.1056/NEJMe078181

Li J, Chen H, Yang S, et al.,2013. Individualized mycophenolate mofetil therapy based on monitoring of mycophenolic acid trough level in cardiac transplant recipients. Chin J Organ Transplant, 34(3): 139-143.

Unedited

https://doi.org/10.3760/cma.j.issn.0254-1785.2013.03.004

Lian J, Feng H, Fang Z, et al., 2017. Research on Results of Plasma Mycophenolic Acid Concentration Detected by EMIT and HPLC in the Patients after Renal Transplantation. J Mod Lab Med, 32(03): 74-78. https://doi.org/10.3969/j.issn.1671-7414.2017.03.020

Liu H, Zhang R, Li R, et al., 2020. Determination of mycophenolic acid in human plasma by LC-MS/MS and its correlation with EMIT. Chin J Clin Pharmacol, 36(22): 3802-3806. https://doi.org/10.13699/j.cnki.1001-6821.2020.22.054

Liu K, Xu T, Jiang X, 2016. Correlations between adverse drug reactions and area under concentration-time curve of mycophenolate mofetil patients received kidney transplantation. Chin J Hosp Pharm, 36(8): 658-661. https://doi.org/10.13286/j.cnki.chinhosppharmacyj.2016.08.15

Liu S, Chen H, Guo Q, et al., 2024. Investigation of patients' preferences regarding therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. China Pharmacy, 35(01): 90-94. https://10.6039/j.issn.1001-0408.2024.01.16

Lopez-Solis R, DeVera M, Steel J, et al., 2014. Gastrointestinal side effects in liver transplant recipients taking enteric-coated mycophenolate sodium vs. mycophenolate mofetil. Clin Transplant, 28(7): 783-788. https://doi.org/10.1111/ctr.12379

Mendez R, 1998. FK 506 and mycophenolate mofetil in renal transplant recipients: six-month results of a multicenter, randomized dose ranging trial. Transplant Proc, 30(4): 1287-1289. https://doi.org/10.1016/s0041-1345(98)00244-9

Miura M, Niioka T, Kato S, et al., 2011. Monitoring of mycophenolic acid predose concentrations in the maintenance phase more than one year after renal transplantation. Ther Drug Monit, 33(3): 295-302. https://doi.org/10.1097/FTD.0b013e3182197e38

Mohammadpur AH, Nazemian F, Abtahi B, et al., 2008. Influence of renal graft function on mycophenolic acid pharmacokinetics during the early period after kidney transplant. Exp Clin Transplant, 6(4): 276-281. https://doi.org/10.1097/MOT.0b013e3283177b56

Musuamba FT, Mourad M, Haufroid V, et al., 2013. Statistical tools for dose individualization of mycophenolic acid and tacrolimus co-administered during the first month after renal transplantation. Br J Clin Pharmacol, 75(5): 1277-1288. https://doi.org/10.1111/bcp.12007

Musuamba FT, Rousseau A, Bosmans JL, et al., 2009. Limited sampling models and Bayesian estimation for mycophenolic acid area under the curve prediction in stable renal transplant patients co-medicated with ciclosporin or sirolimus. Clin Pharmacokinet, 48(11): 745-758. https://doi.org/10.2165/11318060-000000000-00000

Na Takuathung M, Sakuludomkan W, Koonrungsesomboon N, 2021. The Impact of Genetic Polymorphisms on the Pharmacokinetics and Pharmacodynamics of Mycophenolic Acid: Systematic Review and Meta-analysis. Clin Pharmacokinet, 60(10): 1291-1302. https://doi.org/10.1007/s40262-021-01037-7

Naffouje R, Grover P, Yu H, et al., 2019. Anti-Tumor Potential of IMP Dehydrogenase Inhibitors: A Century-Long Story. Cancers (Basel), 11(9): 1346. https://doi.org/10.3390/cancers11091346

Nelson J, Alvey N, Bowman L, et al., 2022. Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation. Pharmacotherapy, 42(8): 599-633. https://doi.org/10.1002/phar.2716

Neylan JF, 1997. Immunosuppressive therapy in high-risk transplant patients: dose-dependent efficacy of mycophenolate mofetil in African-American renal allograft recipients. Transplantation, 64(9): 1277-1282. https://doi.org/10.1097/00007890-199711150-00008

Pawinski T, Kunicki PK, Sobieszczanska-Malek M, et al., 2009. A limited sampling strategy for estimating mycophenolic acid area under the curve in adult heart transplant patients treated with concomitant cyclosporine. J Clin Pharm Ther, 34(1): 89-101. https://doi.org/10.1111/j.1365-2710.2008.00973.x

Pawinski T, Luszczynska P, Durlik M, et al., 2013. Development and validation of limited sampling strategies for the estimation of mycophenolic acid area under the curve in adult kidney and liver transplant recipients receiving concomitant enteric-coated mycophenolate sodium and tacrolimus. Ther Drug Monit, 35(6): 760-769. https://doi.org/10.1097/FTD.0b013e31829b88f5

Peng W, Liu G, Huang H, et al., 2018. Short-Term Intensified Dosage Regimen of Mycophenolic Acid is Associated with Less Acute Rejection in Kidney Transplantation from Donation after Circulatory Death. Urol Int, 101(4): 443-449. https://doi.org/10.1159/000494361

Pichlmayr R, 1995. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. Lancet, 345(8961): 1321-1325. https://doi.org/10.1016/S0140-6736(95)92534-1

Prémaud A, Rousseau A, Le Meur Y, et al., 2004. Comparison of liquid chromatography-tandem mass spectrometry with a commercial enzyme-multiplied immunoassay for the determination of plasma MPA in renal transplant recipients and consequences for therapeutic drug monitoring. Ther Drug Monit, 26(6): 609-619. https://doi.org/10.1097/00007691-200412000-00005

Resztak M, Sobiak J, Czyrski A, 2021. Recent Advances in Therapeutic Drug Monitoring of Voriconazole, Mycophenolic Acid, and Vancomycin: A Literature Review of Pediatric Studies. Pharmaceutics, 13(12): 1991. https://doi.org/10.3390/pharmaceutics13121991

Ribba B, Dudal S, Lavé T, et al., 2020. Model-Informed Artificial Intelligence: Reinforcement Learning for Precision Dosing. Clin

unedited

Pharmacol Ther, 107(4): 853-857. https://doi.org/10.1002/cpt.1777

Romano P, Agena F, de Almeida Rezende Ebner P, et al., 2019. Longitudinal Pharmacokinetics of Mycophenolic Acid in Elderly Renal Transplant Recipients Compared to a Younger Control Group: Data from the nEverOld Trial. Eur J Drug Metab Pharmacokinet, 44(2): 189-199. https://doi.org/10.1007/s13318-018-0506-6

Rong Y, Patel V, Kiang TKL, 2021. Recent lessons learned from population pharmacokinetic studies of mycophenolic acid: physiological, genomic, and drug interactions leading to the prediction of drug effects. Expert Opin Drug Metab Toxicol, 17(12): 1369-1406. https://doi.org/10.1080/17425255.2021.2027906

Saliba F, Rostaing L, Gugenheim J, et al., 2016. Corticosteroid-Sparing and Optimization of Mycophenolic Acid Exposure in Liver Transplant Recipients Receiving Mycophenolate Mofetil and Tacrolimus: A Randomized, Multicenter Study. Transplantation, 100(8): 1705-1713. https://doi.org/10.1097/TP.0000000000001228

Salvadori M, Holzer H, de Mattos A, et al., 2004. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. Am J Transplant, 4(2): 231-236. https://doi.org/10.1046/j.1600-6143.2003.00337.x

Sánchez Fructuoso AI, Perez-Flores I, Calvo N, et al., 2012. Limited-sampling strategy for mycophenolic acid in renal transplant recipients reciving enteric-coated mycophenolate sodium and tacrolimus. Ther Drug Monit, 34(3): 298-305. https://doi.org/10.1097/FTD.0b013e318255cc15

Schünemann HJ, Wiercioch W, Etxeandia I, et al., 2014. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ, 186(3): E123-E142. https://doi.org/10.1503/cmaj.131237

Sekercioglu N, Fu R, Kim SJ, et al., 2021. Machine learning for predicting long-term kidney allograft survival: a scoping review. Ir J Med Sci, 190(2): 807-817. https://doi.org/10.1007/s11845-020-02332-1

Shaw LM, Korecka M, Venkataramanan R, et al., 2003. Mycophenolic acid pharmacodynamics and pharmacokinetics provide a basis for rational monitoring strategies. Am J Transplant, 3(5): 534-542. https://doi.org/10.1034/j.1600-6143.2003.00079.x

Shipkova M, Schütz E, Besenthal I, et al., 2010. Investigation of the crossreactivity of mycophenolic acid glucuronide metabolites and of mycophenolate mofetil in the Cedia MPA assay. Ther Drug Monit, 32(1): 79-85. https://doi.org/10.1097/FTD.0b013e3181cc342a

Sobiak J, Resztak M, 2021. A Systematic Review of Multiple Linear Regression-Based Limited Sampling Strategies for Mycophenolic Acid Area Under the Concentration-Time Curve Estimation. Eur J Drug Metab Pharmacokinet, 46(6): 721-742. https://doi.org/10.1007/s13318-021-00713-0

Sommerer C, Glander P, Arns W, et al., 2011. Safety and efficacy of intensified versus standard dosing regimens of enteric-coated mycophenolate sodium in de novo renal transplant patients. Transplantation, 91(7): 779-785. https://doi.org/10.1097/TP.0b013e31820d3b9b

Squifflet JP, Bäckman L, Claesson K, et al., 2001. Dose optimization of mycophenolate mofetil when administered with a low dose of tacrolimus in cadaveric renal transplant recipients. Transplantation, 72(1): 63-69. https://doi.org/10.1097/00007890-200107150-00014

Tanaka M, Kikuchi M, Takasaki S, et al., 2019. Limited Sampling Strategy for the Estimation of Mycophenolic Acid and its Acyl Glucuronide Metabolite Area under the Concentration-Time Curve in Japanese Lung Transplant Recipients. J Pharm Pharm Sci, 22(1): 407-417. https://doi.org/10.18433/jpps30505

Tang JT, de Winter BC, Hesselink DA, et al., 2017. The pharmacokinetics and pharmacodynamics of mycophenolate mofetil in younger and elderly renal transplant recipients. Br J Clin Pharmacol, 83(4): 812-822. https://doi.org/10.1111/bcp.13154

Ting LS, Partovi N, Levy RD, et al., 2006. Limited sampling strategy for predicting area under the concentration-time curve of mycophenolic acid in adult lung transplant recipients. Pharmacotherapy, 26(9): 1232-1240. https://doi.org/10.1592/phco.26.9.1232

Todorova EK, Huang SH, Kobrzynski MC, et al., 2015. What is the intrapatient variability of mycophenolic acid trough levels? Pediatr Transplant, 19(7): 669-674. https://doi.org/10.1111/petr.12559

van Gelder T, Hilbrands LB, Vanrenterghem Y, et al., 1999. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. Transplantation, 68(2): 261-266. https://doi.org/10.1097/00007890-199907270-00018

van Gelder T, Silva HT, de Fijter H, et al., 2011. How delayed graft function impacts exposure to mycophenolic acid in patients after renal transplantation. Ther Drug Monit, 33(2): 155-164. https://doi.org/10.1097/FTD.0b013e31820c0a96

van Gelder T, Silva HT, de Fijter JW, et al., 2008. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation, 86(8): 1043-1051. https://doi.org/10.1097/TP.0b013e318186f98a

van Gelder T, Vinks AA, 2021. Machine Learning as a Novel Method to Support Therapeutic Drug Management and Precision Dosing. Clin Pharmacol Ther, 110(2): 273-276. https://doi.org/10.1002/cpt.2326

van Hest RM, Mathôt RA, Vulto AG, et al., 2004. Mycophenolic acid in diabetic renal transplant recipients: pharmacokinetics and application of a limited sampling strategy. Ther Drug Monit, 26(6): 620-625.

Unedited

https://doi.org/10.1097/00007691-200412000-00006
Vogl M, Weigel G, Seebacher G, et al., 1999. Evaluation of the EMIT Mycophenolic Acid Assay from Dade Behring. Ther Drug Monit, 21(6): 638-643. https://doi.org/10.1097/00007691-199912000-00010
Wang Z, He JJ, Liu XY, et al., 2015. The evaluation of enteric-coated mycophenolate sodium in cardiac deceased donor liver transplant patients in China. Immunopharmacol Immunotoxicol, 37(6): 508-512. https://doi.org/10.3109/08923973.2015.1096286
Westley IS, Ray JE, Morris RG, 2006. CEDIA mycophenolic acid assay compared with HPLC-UV in specimens from transplant recipients. Ther Drug Monit, 28(5): 632-636. https://doi.org/10.1097/01.ftd.0000243963.53322.8d
Westley IS, Sallustio BC, Morris RG, 2005. Validation of a high-performance liquid chromatography method for the measurement of mycophenolic acid and its glucuronide metabolites in plasma. Clin Biochem, 38(9): 824-829. https://doi.org/10.1016/j.clinbiochem.2005.05.008
Whiting PF, Rutjes AW, Westwood ME, et al., 2011. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med, 155(8): 529-536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009
Woillard JB, Labriffe M, Debord J, et al., 2021. Mycophenolic Acid Exposure Prediction Using Machine Learning. Clin Pharmacol Ther, 110(2): 370-379. https://doi.org/10.1002/cpt.2216
World Health Organization, 2014. WHO Handbook for Guideline Development (2nd ed.). Geneva, Switzerland, p.1-56
Xiang H, Zhou H, Zhang J, et al., 2021. Limited Sampling Strategy for Estimation of Mycophenolic Acid Exposure in Adult Chinese Heart Transplant Recipients. Front Pharmacol, 12: 652333. https://doi.org/10.3389/fphar.2021.652333
Yabuki H, Matsuda Y, Watanabe T, et al., 2020. Plasma mycophenolic acid concentration and the clinical outcome after lung transplantation. Clin Transplant, 34(12): e14088. https://doi.org/10.1111/ctr.14088
Yamada S, Shiohira H, Uehara H, et al., 2016. Implications of Clinical Mycophenolate Mofetil Dose According to Individual Body Weight in Japanese Renal Transplant Recipients. Transplant Proc, 48(1): 35-41. https://doi.org/10.1016/j.transproceed.2015.11.014
Yamani MH, Starling RC, Goormastic M, et al., 2000. The impact of routine mycophenolate mofetil drug monitoring on the treatment of cardiac allograft rejection. Transplantation, 69(11): 2326-2330. https://doi.org/10.1097/00007890-200006150-00018
Yang Y, Zhou P, Xu D, et al., 2014. Reducing dosage of corticosteroid by mycophenolate acid therapeutic drug monitoring for renal allograft recipients. Journal of Shanghai Jiaotong University (Medical Science), 34(10): 1534-1538. https://doi.org/10.3969/j.issn.1674-8115.2014.10.024
Yao X, Huang H, Wei C, et al., 2015. Limited Sampling Strategy for Mycophenolic Acid in Chinese Kidney Transplant Recipients Receiving Enteric-Coated Mycophenolate Sodium and Tacrolimus During the Early Posttransplantation Phase. Ther Drug Monit, 37(4): 516-523. https://doi.org/10.1097/FTD.0000000000000170
Ye Z, Reintam Blaser A, Lytvyn L, et al., 2020. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. BMJ, 368: l6722. https://doi.org/10.1136/bmj.l6722
Yeung JS, Wang W, Chan L, 1999. Determination of mycophenolic acid level: comparison of high-performance liquid chromatography with homogeneous enzyme-immunoassay. Transplant Proc, 31(1-2): 1214-1215. https://doi.org/10.1016/s0041-1345(98)01968-x
Yin T, Liang H, Huang Q, et al., 2023. A Survey of Therapeutic Drug Monitoring Status in China. Ther Drug Monit, 45(2): 151-158. https://doi.org/10.1097/FTD.0000000000001060
Yu ZC, Zhang WX, Chen Hao, et al., 2007. Limited sampling strategy for the estimation of mycophenolic acid area under the plasma concentration-time curve in adult patients undergoing liver transplant. Ther Drug Monit, 29(2): 207-214. https://doi.org/10.1097/FTD.0b013e318040ce0b
Zeng L, Yi Q, Huang L, et al., 2022. The guideline for therapeutic drug monitoring guidelines development. J Evid Based Med, 15(3): 272-283. https://doi.org/10.1111/jebm.12486
Zeng W, Zhang C, Song M, et al., 2018. Effect of mycophenolate mofetil and enteric-coated mycophenolate sodium on blood concentration in renal transplantrecipients. Organ Transplantation, 9(06): 436-440. https://doi.org/10.3969/j.issn.1674-7445.2018.06.007
Zhang H, Liu L, Li J, et al., 2016. The efficacy and safety of intensified enteric-coated mycophenolate sodium with low exposure of calcineurin inhibitors in Chinese de novo kidney transplant recipients: a prospective study. Int J Clin Pract, 70 Suppl 185: 22-30. https://doi.org/10.1111/ijcp.12813
Zhang HX, Sheng CC, Liu LS, et al., 2019. Systematic external evaluation of published population pharmacokinetic models of mycophenolate mofetil in adult kidney transplant recipients co-administered with tacrolimus. Br J Clin Pharmacol, 85(4): 746-761. https://doi.org/10.1111/bcp.13850
Zhang J, Sun Z, Zhu Z, et al., 2018. Pharmacokinetics of Mycophenolate Mofetil and Development of Limited Sampling Strategy in Early Kidney Transplant Recipients. Front Pharmacol, 9: 908. https://doi.org/10.3389/fphar.2018.00908
Zhang X, Li H, Wang W, et al., 2014. Comparison of pharmacokinetics and clinical application in patients given enteric-coated

unedited

mycophenolate sodium or mycophenolate mofetil after renal transplantation. Chin J Organ Transplant, 35(8): 464-468. https://doi.org/10.3760/cma.j.issn.0254-1785.2014.08.005

Zhou PJ, Xu D, Yu ZC, et al., 2007. Pharmacokinetics of mycophenolic acid and estimation of exposure using multiple linear regression equations in Chinese renal allograft recipients. Clin Pharmacokinet, 46(5): 389-401. https://doi.org/10.2165/00003088-200746050-00002

Supplementary information

Supplementary Appendix

unedited