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

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Abstract: 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. The guideline plan was drawn 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. 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 (C_0), 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. 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 (MPA); Therapeutic drug monitoring (TDM); Grading of Recommendations Assessment, Development, and Evaluation (GRADE); Solid organ transplant

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 is 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 HealThcare (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), with the 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, China National Knowledge Infrastructure (CNKI), WANFANG database, SinoMed, and ClinicalTrials.gov. In total, 36 043 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 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

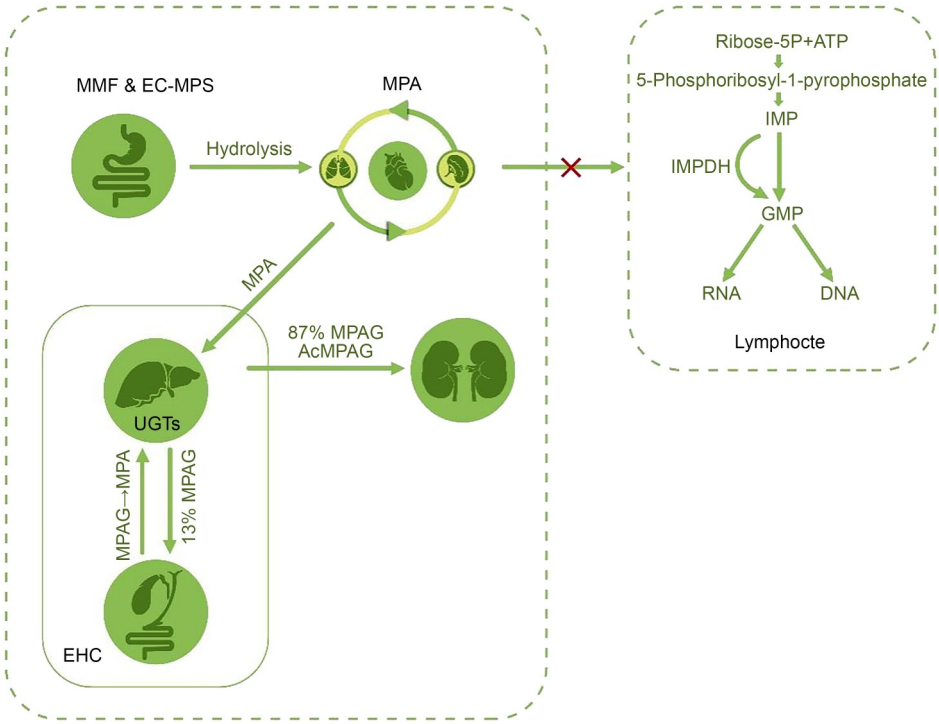

Fig. 1 Pharmacokinetic and pharmacodynamic pathways of mycophenolic acid (MPA). MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium; MPAG: 7-*O*-MPA-glucuronide; UGTs: UDP-glycosyltransferases; EHC: enterohepatic (re)circulation; AcMPAG: acyl-MPAG; ATP: adenosine triphosphate; IMP: inositol-1-phosphate; IMPDH: inosine monophosphate dehydrogenase; GMP: guanosine-5'-monophosphate.

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.

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 statement (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.

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

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, and 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 ten high-quality studies (le Meur et al., 2007, 2011; van Gelder et al., 2008; Gaston et al., 2009; Kamar et al., 2009; 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

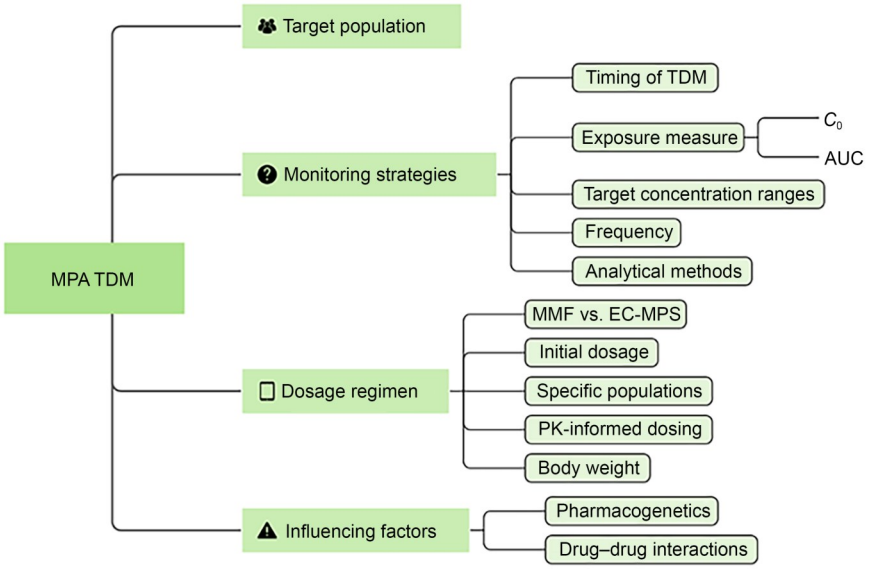

Fig. 2 Framework of the guideline for the therapeutic drug monitoring (TDM) of mycophenolic acid (MPA). C_0: trough concentration; AUC: area under the curve; MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium; PK: pharmacokinetic.

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

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

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: Only three high-quality studies were included in the systematic review as insufficient direct comparative evidence was available (Dösch et al., 2006; Miura et al., 2011; Todorova et al., 2015). 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.

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

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, and is influenced by factors such as enterohepatic circulation (Holt, 2002; Arns et al., 2005; Ettenger et al., 2005). Furthermore, steady-state plasma MPA concentrations are typically achieved after a treatment duration of 7 d (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, 2013; Pawinski et al., 2009, 2013; Capone et al., 2011; Sánchez Fructuoso et al., 2012; 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. In the literature, 2 to 4 sampling points were most commonly used for LSS. The most commonly used sampling point for MMF is C_2 (blood concentration at 2 h post-dose). 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 (blood concentration at 8 h post-dose). For EC-MPS, the first peak concentration is found 1.50–2.75 h post-administration, and the most commonly used sampling points are C_1 (blood concentration at 1 h post-dose) 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 (blood concentrations at 6, 8, and 9 h post-dose, respectively). Including these LSS formulas in clinical practice is recommended after further validation and assessment in independent patient populations.

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

Recommendation 5: The recommended C_0 monitoring ranges for MPA in different solid organ transplantation types are shown in Table 2.

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

Evidence summary: This systematic review included eight studies (van Gelder et al., 1999, 2008; Yamani et al., 2000; Kuypers et al., 2008; Jiang et al., 2015; Liu et al., 2016; Jung et al., 2020; Yabuki et al., 2020), including two randomized controlled trials (RCTs) and six cohort studies. Qualitative analysis

Table 2 Recommended C_0 ranges

Solid organ transplant	C_0 (mg/L)	Strength of recommendation	Certainty of evidence
Renal transplant	<3.5	Weak	Low
Heart transplant	>2.0	Weak	Low
Liver transplant	1.0–3.5	GPS	GPS
Lung transplant		Lack of high-quality evidence, not yet recommended	

C_0: trough concentration; GPS: good practice statement.

Table 3 Recommended AUC ranges

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

AUC: area under the curve; GPS: good practice statement.

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 2.0 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 are currently insufficient data to support an evidence-based MPA C_0 target in lung transplant recipients.

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 occurs. (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 one or two 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 with monthly monitoring, 17.14% preferred bi-monthly monitoring, 14.29% chose monitoring every three months, and 31.43% believed that monitoring should be performed only when clinically necessary.

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 required, immunoassays such as enzyme multiplied immunoassay technique (EMIT), particle-enhanced turbidimetric inhibition immunoassay (PETINIA), or cloned enzyme donor immunoassay (CEDIA) can also be used 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, 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, owing to cross-reactivity with MPA metabolites, the immunoassay measured higher MPA concentrations compared to chromatography, and the mean bias decreased as MPA concentration increased, with liver transplant exhibiting the largest positive bias. For renal transplant recipients undergoing 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

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: The systematic review 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.

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 nine studies (European Mycophenolate Mofetil Cooperative Study Group, 1995; The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group, 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 six were RCTs and three were cohort studies. Four RCTs compared the effectiveness and safety of high-dose versus standard-dose immunosuppression in 1128 adult renal transplant recipients. Meta-analysis results indicated that the incidence of BPAR confirmed by biopsy in the high-dose group (1.5 g twice a day (bid) or 1.5 g bid for 1–5 d 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, five studies compared the effectiveness and safety of

low-dose versus standard-dose immunosuppression in 755 adult renal transplant recipients, including two RCTs and three cohort studies. Meta-analysis results indicated that the incidence of BPAR confirmed by biopsy in the low-dose group (1.0 g/d or 1.0–1.5 g/d) was significantly higher than that in the control group (RR=2.94, 95% CI (1.51–5.73), P=0.001).

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 five studies (Glander et al., 2010; Sommerer et al., 2011; Ding et al., 2014; Zhang et al., 2016; Peng et al., 2018), three of which were RCTs and two were cohort studies. Of note, four 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 (0.69–0.98), P=0.03). No statistically significant differences were found in other outcomes between the two groups. In total, one RCT included 60 renal transplant recipients and revealed no significant differences in efficacy or safety between low-dose and standard-dose EC-MPS.

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 two 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.

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 eight 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.

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 PPK 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

Table 4 Recommendations for special populations

Special population	Recommendation	Strength of recommendation	Certainty of evidence
Child	Age under 6 years 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	Mycophenolic acid (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 dosage adjustment.	Weak	Moderate
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

investigate the key factors affecting the predictability of MMF models by including potential covariates.

3.4 Pharmacogenetics and drug–drug interactions

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

Recommendation 15: Routine genetic monitoring is not recommended for patients on MPA. (1D: strong, very low)

Evidence summary: A systematic review (Na Takuathung et al., 2021) found no significant association between single nucleotide polymorphisms (SNPs), including those in IMPDH genes, and MPA clinical efficacy. *SLCO1B3 334T>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. Compared with wild-type individuals, *UGT1A9−275T>A* carriers exhibited significantly lower C_0, maximum concentration (C_{max}), and AUC from 0 to 12 h (AUC_{0-12}), with significantly higher apparent clearance (CL/F). Gene testing has limited value in guiding individualized MMF therapy, and dose adjustments according to gene testing results are not recommended.

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

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 effects 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 (Eckardt et al., 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 C_0 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

Table 5 Management of co-administered drugs of MPA

Drug interaction	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 2 h 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, and metronidazole	MMF, EC-MPS	↓	Impaired EHRC	Strengthen drug monitoring
Cyclosporine	MMF, EC-MPS	↓	Impaired EHRC	Strengthen drug monitoring
Isavuconazole	MMF, EC-MPS	↑	Inhibited glucuronidation	Strengthen drug monitoring
Telmisartan	MMF	↓	Induced glucuronidation	Strengthen drug monitoring
Acyclovir and 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.

MPA, initial dosage regimens, special patient populations, PK-informed dosing, considerations associated with body weight factors, pharmacogenetic aspects, and potential drug–drug interactions.

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 attitudes of patients toward the TDM of MPA and its associated determinants. Impressively, 82.86% of the 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 PPK 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/pharmacodynamic (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, owing to the lack of evidence of the cost-effectiveness of TDM of MPA, its economic effects have not been comprehensively studied in different countries.

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.

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Author contributions

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, conducting literature retrieval, evaluation, synthesis, and grading of evidence, performing 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, and 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. Shuang LIU, Hongsheng CHEN, Zaiwei SONG, Qi GUO, Xianglin ZHANG, Bingyi SHI, Suodi ZHAI, Lingli ZHANG, Liyan MIAO, 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, and Rongsheng ZHAO declare that they have no conflicts of interest.

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Supplementary information

Supplementary Appendix