# Supplementary Appendix

## Part I The detail list of panel members

***Working group of the guidelines***

This establishment of the guidelines was initiated by the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. The guideline development team consisted of four groups. A guideline working group was established consisting of a multidisciplinary panel of experts involved in solid organ transplants, such as clinical pharmacists, clinical physicians, and evidence-based medicine experts. The responsibilities of the steering committee were to draft the scope of the guidelines, manage evidence retrieval, and finalize the guidelines. The guideline development group was responsible for evidence retrieval and synthesis, drafting the final recommendations, and taking diverse values and preferences into consideration. The external group was tasked to review the guideline document when recommendations were finalized.

| **Name** | **Title** | **Affiliation** | **Major** |
|---|---|---|---|
| **Chair** | | | |
| **Rongsheng Zhao** | Professor | Peking University Third Hospital | Clinical Pharmacy |
| **Steering Committee** | | | |
| Xianglin Zhang | Chief Pharmacist/Professor | China-Japan Friendship Hospital | Pharmacology |
| Bingyi Shi | Professor | The 8th Medical Center of Chinese People's Liberation Army General Hospital | Organ Transplantation |
| Suodi Zhai | Chief Pharmacist/Professor | Peking University Third Hospital | Clinical Pharmacy |
| Lingli Zhang | Chief | West China Second University Hospital, Sichuan University | Evidence-based Medicine |

| | | | |
|---|---|---|---|
| | Pharmacist/Professor | | |
| Liyan Miao | Chief Pharmacist/Professor | The First Affiliated Hospital of Soochow University | Clinical Pharmacy |
| **Consensus Panel** | | | |
| Wujun Xue | Professor | The First Affiliated Hospital of Xi'an Jiaotong University | Organ Transplantation |
| Jianyong Wu | Professor | The First Affiliated Hospital, Zhejiang University School of Medicine | Organ Transplantation |
| Changxi Wang | Professor | The First Affiliated Hospital, Sun Yat-sen University | Organ Transplantation |
| Lulin Ma | Professor | Peking University Third Hospital | Urology |
| Xiaofei Hou | Professor | Peking University Third Hospital | Urology |
| Wei Wang | Professor | Beijing Chao-Yang Hospital, Capital Medical University | Urology |
| Tao Lin | Professor | West China Hospital, Sichuan University | Urology |
| Long Liu | Professor | General Hospital of Northern Theater Command | Urology |
| Liyan Cui | Professor | Peking University Third Hospital | Laboratory Medicine |
| Ting Xu | Professor | West China Hospital, Sichuan University | Evidence-based Medicine |
| Maobai Liu | Professor | Fujian Medical University Union Hospital | Pharmacoeconomics |
| Limei Zhao | Chief Pharmacist/Professor | Shengjing Hospital of China Medical University | Clinical Pharmacy |
| Qingchun Zhao | Chief Pharmacist/Professor | General Hospital of Northern Theater Command | Clinical Pharmacy |
| Lihong Liu | Chief Pharmacist/Professor | China-Japan Friendship Hospital | Clinical Pharmacy |
| Yi Zhang | Chief Pharmacist/Professor | Tianjin First Central Hospital | Clinical Pharmacy |
| Guanren Zhao | Chief | The 8th Medical Center of Chinese People's Liberation Army General | Clinical Pharmacy |

| | | | |
|---|---|---|---|
| | Pharmacist/Professor | Hospital | |
| Xiaoyang Lu | Chief Pharmacist/Professor | The First Affiliated Hospital, Zhejiang University School of Medicine | Clinical Pharmacy |
| Ling Jiang | Chief Pharmacist/Professor | The First Affiliated Hospital of University of Science and Technology of China | Clinical Pharmacy |
| Weihong Ge | Chief Pharmacist/Professor | Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School | Clinical Pharmacy |
| Zhuo Wang | Chief Pharmacist/Professor | The First Hospital Affiliated to Army Medical University | Clinical Pharmacy |
| Xiao Chen | Chief Pharmacist/Professor | The First Affiliated Hospital, Sun Yat-sen University | Clinical Pharmacy |
| Yu Zhang | Chief Pharmacist/Professor | Union Hospital, Huazhong University Science and Technology | Clinical Pharmacy |
| Bikui Zhang | Chief Pharmacist/Professor | The Second Xiangya Hospital of Central South University | Clinical Pharmacy |
| Xiaojian Zhang | Chief Pharmacist/Professor | The First Affiliated Hospital of Zhengzhou University | Clinical Pharmacy |
| Yalin Dong | Chief Pharmacist/Professor | The First Affiliated Hospital of Xi'an Jiaotong University | Clinical Pharmacy |
| Jun Zhang | Chief Pharmacist/Professor | The First Affiliated Hospital of Kunming Medical University | Clinical Pharmacy |
| **External Review Group (including doctors, nurses, clinical pharmacists and patients)** | | | |
| Wenqian Chen, et al. | | China-Japan Friendship Hospital | Clinical Pharmacy, renal transplant |
| Wenjing Hou, et al. | | Beijing Friendship Hospital, Capital Medical University | Clinical Pharmacy, renal transplant |
| Kuifen Ma, et al. | | The First Affiliated Hospital, Zhejiang University School of Medicine | Clinical Pharmacy, renal transplant |

| | | | |
|---|---|---|---|
| Houwen Lin, et al. | | Renji Hospital, Shanghai Jiao Tong University of Medicine | Clinical Pharmacy, renal transplant |
| Han Yan, et al. | | The Second Xiangya Hospital of Central South University | Clinical Pharmacy, renal transplant |
| Chen Shi, et al. | | *Union Hospital, Tongji Medical College, Huazhong University of Science and Technology* | Clinical Pharmacy, renal transplant |
| Pan Chen, et al. | | The First Affiliated Hospital, Sun Yat-sen University | Clinical Pharmacy, renal transplant |
| Weiyi Feng, et al. | | The First Affiliated Hospital of Xi'an Jiaotong University | Clinical Pharmacy, renal transplant |
| Feng Qiu, et al. | | The First Affiliated Hospital of Chongqing Medical University | Clinical Pharmacy, renal transplant |
| Yanqing Song, et al | | The First Bethune Hospital of Jilin University | Clinical Pharmacy, renal transplant |
| **Evidence Synthesis Team** | | | |
| Shuang Liu | Clinical Pharmacist | Peking University Third Hospital | Clinical Pharmacy |
| Hongsheng Chen | Master Candidate | Peking University Third Hospital | Clinical Pharmacy |
| Qi Guo | Master Candidate | Peking University Third Hospital | Clinical Pharmacy |
| Zaiwei Song | Pharmacist in charge | Peking University Third Hospital | Clinical Pharmacy |
| Guanru Wang | Master | Peking University Third Hospital | Clinical Pharmacy |
| Yang Hu | Doctor Candidate | Peking University Third Hospital | Clinical Pharmacy |
| Dan Jiang | Doctor Candidate | Peking University Third Hospital | Clinical Pharmacy |

# Part II Search Strategy (Feb, 2023)

**Table S1. Search terms used in the main review for English-language databases**

| | Pubmed | Embase | The Cochrane Library | Clinical trials.gov |
|---|---|---|---|---|
| **1. MPA** | | | | |
| | (Mycophenolic Acid"[MeSH Terms]) OR (Mycophenolic Acid[Text Word]) OR (Mycophenolate Mofetil[Text Word]) OR (Mycophenylate mofetil [Text Word]) OR (Mycophenolate [Text Word]) OR (Cellcept[Text Word]) OR (Myfortic[Text Word]) OR (MMF[Title/Abstract]) OR (EC-MPS [Title/Abstract]) OR (MPA[Title/Abstract]) OR (RS 61443[Text Word]) | 'Mycophenolic Acid '/exp OR 'Mycophenolic Acid':ab,ti OR 'Mycophenolate Mofetil '/exp OR 'Mycophenylate mofetil':ab,ti OR 'Mycophenolate ':ab,ti OR 'Cellcept':ab,ti OR 'Myfortic':ab,ti OR 'MMF':ab,ti OR 'EC-MPS':ab,ti OR 'MPA':ab,ti OR 'RS 61443 ':ab,ti | 'Mycophenolic Acid' [Mesh] OR 'Mycophenolic Acid':ti,ab,kw OR 'Mycophenylate mofetil':ti,ab,kw OR 'Mycophenolate':ti,ab,kw OR 'Cellcept':ti,ab,kw OR 'Myfortic':ti,ab,kw OR 'MMF':ti,ab,kw OR 'EC-MPS':ti,ab,kw OR 'MPA':ti,ab,kw OR 'RS 61443':ti,ab,kw | Mycophenolate Mofetil<br>Cellcept<br>Munoloc<br>Mycophenolate<br>Mycophenolate Mofetil Hydrochloride<br>Mycophenolic Acid<br>Myfortic<br>ERL080 |
| **2.Therapeutic Drug Monitoring** | | | | |
| | (drug monitoring[MeSH Terms]) OR (drug monitoring[Text Word]) OR (therapeutic monitoring[Text Word]) OR (serum concentration monitoring[Text Word]) OR (therapeutic drug[Text Word]) OR (medication monitoring[Text Word]) OR (monitors medication[Text Word]) OR (blood level[Text Word]) OR (drug level[Text Wor | 'drug monitoring'/exp OR 'therapeutic monitoring':ab,ti OR 'serum concentration monitoring':ab,ti OR therapeutic drug':ab,ti OR 'medication monitoring':ab,ti OR 'monitors medication ':ab,ti OR 'blood level'/exp OR 'drug concentration'/exp OR 'plasma concentration-time curve'/exp OR 'drug level':ab,ti OR 'plasma level':ab,ti OR | 'drug Monitoring[Mesh]' OR 'drug monitoring':ti,ab,kw OR 'therapeutic monitoring':ti,ab,kw OR 'serum concentration monitoring':ti,ab,kw OR 'therapeutic drug':ti,ab,kw OR 'medication monitoring':ti,ab,kw OR 'monitors medication':ti,ab,kw OR 'blood level':ti,ab,kw OR 'drug level':ti,ab,kw OR 'plasma level':ti,ab,kw OR 'seru | Therapeutic drug monitoring<br>TDM<br>Therapeutic monitoring<br>Therapeutic drug<br>serum concentration monitoring |

| | | | | |
|---|---|---|---|---|
| | d]) OR (plasma level[Text Word]) OR (serum level[Text Word]) OR (steady state[Text Word]) OR (TDM[Title/Abstract]) OR (pharmacokinetics[Title/Abstract]) OR (Cmax[Title/Abstract]) OR (Cmin[Title/Abstract]) OR (Tmax[Title/Abstract]) OR (AUC[Title/Abstract]) OR (clearance[Title/Abstract]) OR (concentration[Title/Abstract]) | 'serum level':ab,ti OR 'steady state':ab,ti OR 'TDM':ab,ti OR 'Pharmacokinetics':ab,ti OR 'Cmax':ab,ti OR 'Cmin':ab,ti OR 'Tmax':ab,ti OR 'AUC':ab,ti OR 'clearance':ab,ti OR 'concentration':ab,ti | m level':ti,ab,kw OR 'steady state':ti,ab,kw OR 'TDM':ti,ab,kw OR 'Pharmacokinetics':ti,ab,kw OR 'Cmax':ti,ab,kw OR 'Cmin':ti,ab,kw OR 'Tmax':ti,ab,kw OR 'AUC':ti,ab,kw OR 'clearance':ti,ab,kw OR 'concentration':ti,ab,kw | |
| **3. Human** | | | | |
| | (humans[Filter]) | [humans]/lim | Not applicable | Not applicable |
| **Final Search** | | | | |
| | 1 AND 2 AND 3 | 1 AND 2 AND 3 | 1 AND 2 | 1 AND 2 |

**Table S2. Search terms used in the main review for Chinese-language databases**

| | CNKI | WANFANG | Sinomed |
|---|---|---|---|
| **1. MPA** | | | |
| | (TI='霉酚酸' OR AB='霉酚酸' OR TI='麦考酚酸' OR AB='麦考酚酸' OR TI='吗替麦考酚酯' OR AB='吗替麦考酚酯' OR TI='麦考酚吗乙酯' OR AB='麦考酚吗乙酯' OR TI='吗考酚酯' OR AB='吗考酚酯' OR TI='骁悉' OR AB='骁悉' OR TI='赛可平' OR AB='赛可平' OR TI='米芙' OR AB='米芙' ) | (题名: 霉酚酸 or 摘要: 霉酚酸 or 题名: 麦考酚酸 or 摘要: 麦考酚酸 or 题名: 吗替麦考酚酯 or 摘要: 吗替麦考酚酯 or 题名: 麦考酚吗乙酯 or 摘要: 麦考酚吗乙酯 or 题名: 吗考酚酯 or 摘要: 吗考酚酯 or 题名: 麦考酚钠 or 摘要: 麦考酚钠 or 题名: 骁悉 or 摘要: 骁悉 or 题名: 赛可平 or 摘要: 赛可平 or 题名: 米芙 or 摘要: 米芙) | ("霉酚酸" [标题:智能] OR "霉酚酸" [摘要:智能] OR "麦考酚酸" [标题:智能] OR "麦考酚酸" [摘要:智能] OR "吗替麦考酚酯" [标题:智能] OR "吗替麦考酚酯" [摘要:智能] OR "麦考酚吗乙酯" [标题:智能] OR "麦考酚吗乙酯" [摘要:智能] OR "吗考酚酯" [标题:智能] OR "吗考酚酯" [摘要:智能] OR "麦考酚钠" [标题:智能] OR "麦考酚钠" [摘要:智能] OR "骁悉" [标题:智能] OR "骁悉" [摘要:智能] OR "赛可平" [标题:智能] OR "赛可平" [摘要:智能] OR "米芙" [标题:智能] OR "米芙" [摘要:智能]) |
| **2.Therapeutic Drug Monitoring** | | | |
| | TI='药物监测' OR AB='药物监测' OR TI='浓度' OR AB='浓度' OR TI='水平' OR AB='水平' OR TI='药代动力学' OR AB='药代动力学' OR TI='药动学' OR AB='药动学' OR TI='稳态' OR AB='稳态' OR TI='代谢' OR AB='代谢' OR TI='排泄' OR AB='排泄' OR TI='清除' OR AB='清除' OR TI='消除' OR AB='消除' OR TI='TDM' OR AB='TDM' | (题名: 药物监测 or 摘要: 药物监测 or 题名: 浓度 or 摘要: 浓度 or 题名: 水平 or 摘要: 水平 or 题名: 药代动力学 or 摘要: 药代动力学 or 题名: 药动学 or 摘要: 药动学 or 题名: 稳态 or 摘要: 稳态 or 题名: 代谢 or 摘要: 代谢 or 题名: 排泄 or 摘要: 排泄 or 题名: 清除 or 摘要: 清除 or 题名: 消除 or 摘要: 消除 or 题名: TDM or 摘要: TDM) | ("药物监测" [标题:智能] OR "药物监测" [摘要:智能] OR "浓度" [标题:智能] OR "浓度" [摘要:智能] OR "水平" [标题:智能] OR "水平" [摘要:智能] OR "药代动力学" [标题:智能] OR "药代动力学" [摘要:智能] OR "药动学" [标题:智能] OR "药动学" [摘要:智能] OR "稳态" [标题:智能] OR "稳态" [摘要:智能] OR "代谢" [标题:智能] OR "代谢" [摘要:智能] OR "排泄" [标题:智能] OR "排泄" [摘要:智能] OR "清除" [标题:智能] OR "清除" [摘要:智 |

| | | | |
|---|---|---|---|
| | | | 能] OR "消除" [标题:智能] OR "消除" [摘要:智能] OR "TDM" [标题:智能] OR "TDM" [摘要:智能]) |
| **3. Article Type** | | | |
| | 期刊论文 AND 学位论文 | 期刊论文 AND 学位论文 | Not applicable |
| **Final Search** | | | |
| | 1 AND 2 AND 3 | 1 AND 2 AND 3 | 1 AND 2 |

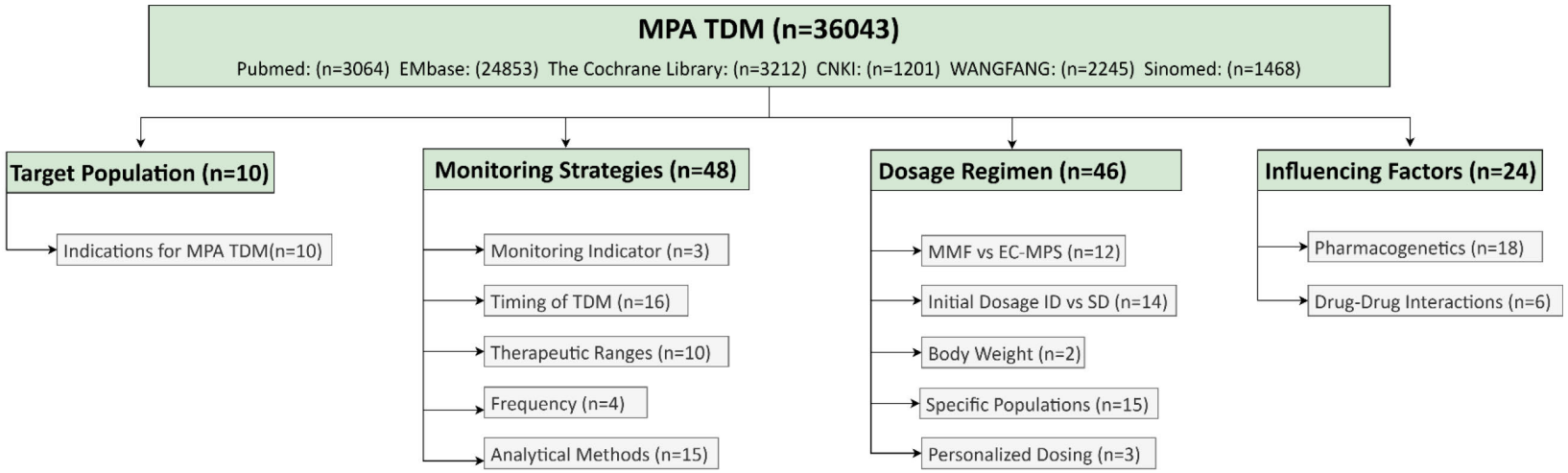



**Fig. 1 The framework of literature search and review summary**

# Part III Clinical questions, results of meta-analysis and quality of evidence in Clinical practice guideline for mycophenolic acid therapeutic drug monitoring in solid organ transplantation

The first panel meeting confirmed the clinical question, participants (P), intervention (I), comparison (C), outcome (O), and study design (S). Finally, 17 clinical questions were included and defined.

## Recommendation 1

## Question 1*: What are the indications for the therapeutic drug monitoring(TDM) of mycophenolic acid (MPA)?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Solid organ transplantation recipients treated with MPA | Receive TDM | Do not receive TDM | Clinical efficacy and safety |

**Table1 The efficacy and safety comparison of TDM or not**

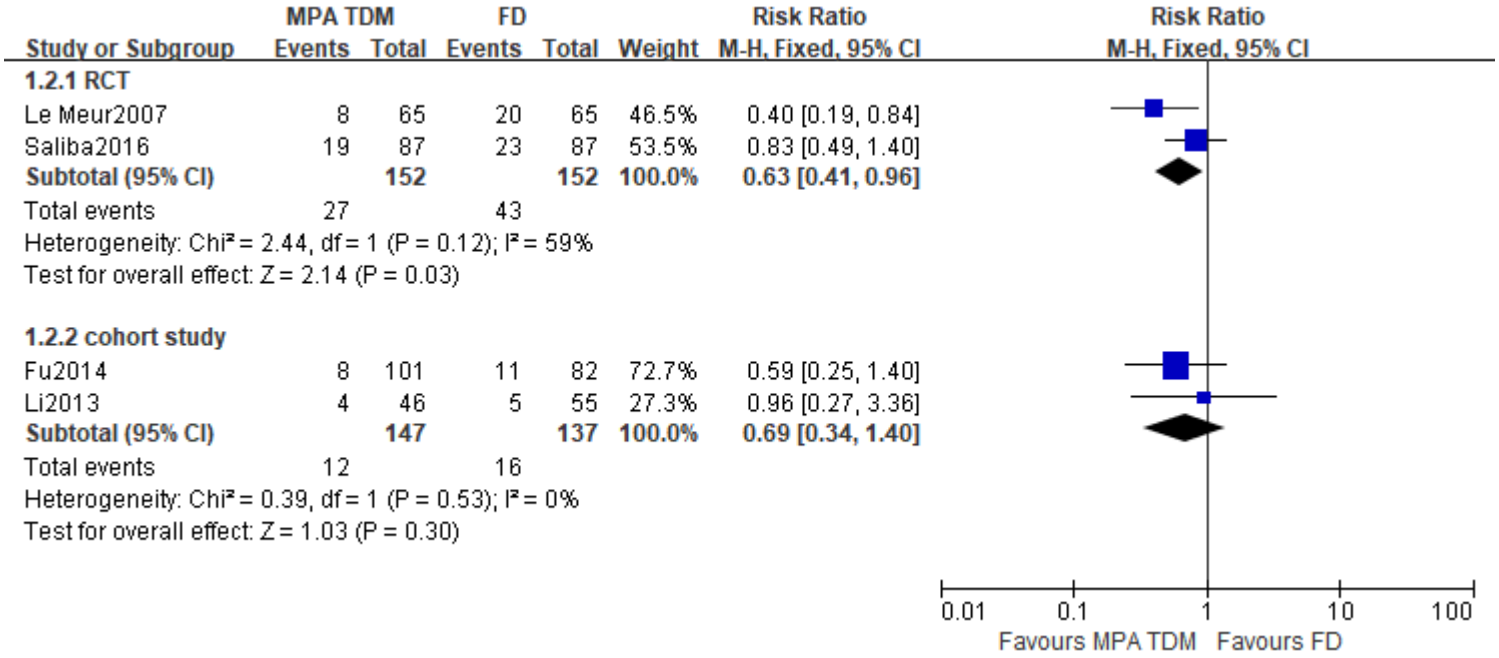
| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **Treatment failure**<br>3 RCTs [1,2,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 201/751 | 214/757 | 0.95 [0.80, 1.11] | Moderate<br>⊕⊕⊕○ |
| **Treatment failure**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 9/101 | 12/82 | 0.61 [0.27, 1.37] | Very low<br>⊕○○○ |
| **AR**<br>2 RCTs [2,5] | Not serious | Serious | Not serious | Serious | Undetected | None | 27/152 | 43/152 | 0.63 [0.41, 0.96] | Low<br>⊕⊕○○ |
| **AR**<br>2 cohort studies [4,6] | Not serious | Not serious | Not serious | Serious | Undetected | None | 12/147 | 16/137 | 0.69 [0.34, 1.40] | Moderate<br>⊕⊕⊕○ |
| **BPAR** | Not serious | Serious | Not serious | Serious | Undetected | None | 136/964 | 139/965 | 0.98 [0.78, 1.22] | Low |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| 5 RCTs [1,2,3,5,7] | | | | | | | | | | ⊕⊕○○ |
| **BPAR**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 4/101 | 7/82 | 0.46 [0.14, 1.53] | Very low<br>⊕○○○ |
| **Death**<br>5 RCTs [1,2,3,7,8] | Not serious | Not serious | Not serious | Serious | Undetected | None | 19/917 | 26/918 | 0.74 [0.41, 1.31] | Moderate<br>⊕⊕⊕○ |
| **Death**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 1/101 | 0/82 | 2.44 [0.10, 59.14] | Very low<br>⊕○○○ |
| **Graft loss**<br>5 RCTs [1,2,3,7,8] | Not serious | Not serious | Not serious | Serious | Undetected | None | 30/917 | 40/918 | 0.75 [0.48, 1.19] | Moderate<br>⊕⊕⊕○ |
| **Graft loss**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 0/101 | 1/82 | 0.27 [0.01, 6.57] | Very low<br>⊕○○○ |
| **MMF discontinuation**<br>4 RCTs [1,2,3,7] | Not serious | Not serious | Not serious | Serious | Undetected | None | 62/877 | 55/878 | 1.13 [0.80, 1.61] | Moderate<br>⊕⊕⊕○ |
| **MMF discontinuation**<br>1 cohort study[4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 1/101 | 0/82 | 2.44 [0.10, 59.14] | Very low<br>⊕○○○ |
| **Infection**<br>3 RCTs [1,2,8] | Not serious | Not serious | Not serious | Serious | Undetected | None | 105/338 | 102/343 | 1.04 [0.86, 1.24] | Moderate<br>⊕⊕⊕○ |
| **Infection**<br>2 cohort studies [4,6] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 24/147 | 43/137 | 0.52 [0.33, 0.81] | Low<br>⊕⊕○○ |
| **Bacterial infection**<br>3 RCTs [2,5,7] | Not serious | Not serious | Not serious | Serious | Undetected | None | 142/283 | 134/282 | 1.06 [0.89, 1.25] | Moderate<br>⊕⊕⊕○ |
| **Bacterial infection**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 8/101 | 10/82 | 0.65 [0.27, 1.57] | Very low<br>⊕○○○ |
| **Leukopenia**<br>6 RCTs [1,2,3,5,7,8] | Not serious | Serious | Not serious | Serious | Undetected | None | 205/1005 | 172/1012 | 1.20 [1.01, 1.44] | Low<br>⊕⊕○○ |
| **Leukopenia**<br>1 cohort study [6] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 3/46 | 10/55 | 0.36 [0.10, 1.23] | Very low<br>⊕○○○ |
| **Anemia**<br>5 RCTs [2,3,5,7,8] | Not serious | Not serious | Not serious | Serious | Undetected | None | 276/772 | 243/774 | 1.14 [1.01, 1.28] | Moderate<br>⊕⊕⊕○ |
| **Anemia**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 52/101 | 46/82 | 0.92 [0.70, 1.20] | Very low<br>⊕○○○ |
| **Diarrhea**<br>4 RCTs [1,3,5,7] | Not serious | Not serious | Not serious | Serious | Undetected | None | 266/900 | 246/907 | 1.09 [0.95, 1.26] | Moderate<br>⊕⊕⊕○ |
| **Diarrhea**<br>2 cohort studies [4,6] | Not serious | Not serious | Not serious | Serious | Undetected | None | 24/147 | 25/137 | 0.85 [0.51, 1.41] | Very low<br>⊕○○○ |
| **Hyperglycemia**<br>4 RCTs [1,5,7,8] | Not serious | Not serious | Not serious | Serious | Undetected | None | 65/491 | 66/495 | 0.99 [0.72, 1.36] | Moderate<br>⊕⊕⊕○ |
| **Virus infection** | Not serious | Not serious | Not serious | Serious | Undetected | None | 19/131 | 19/132 | 1.01 [0.57, 1.80] | Moderate |

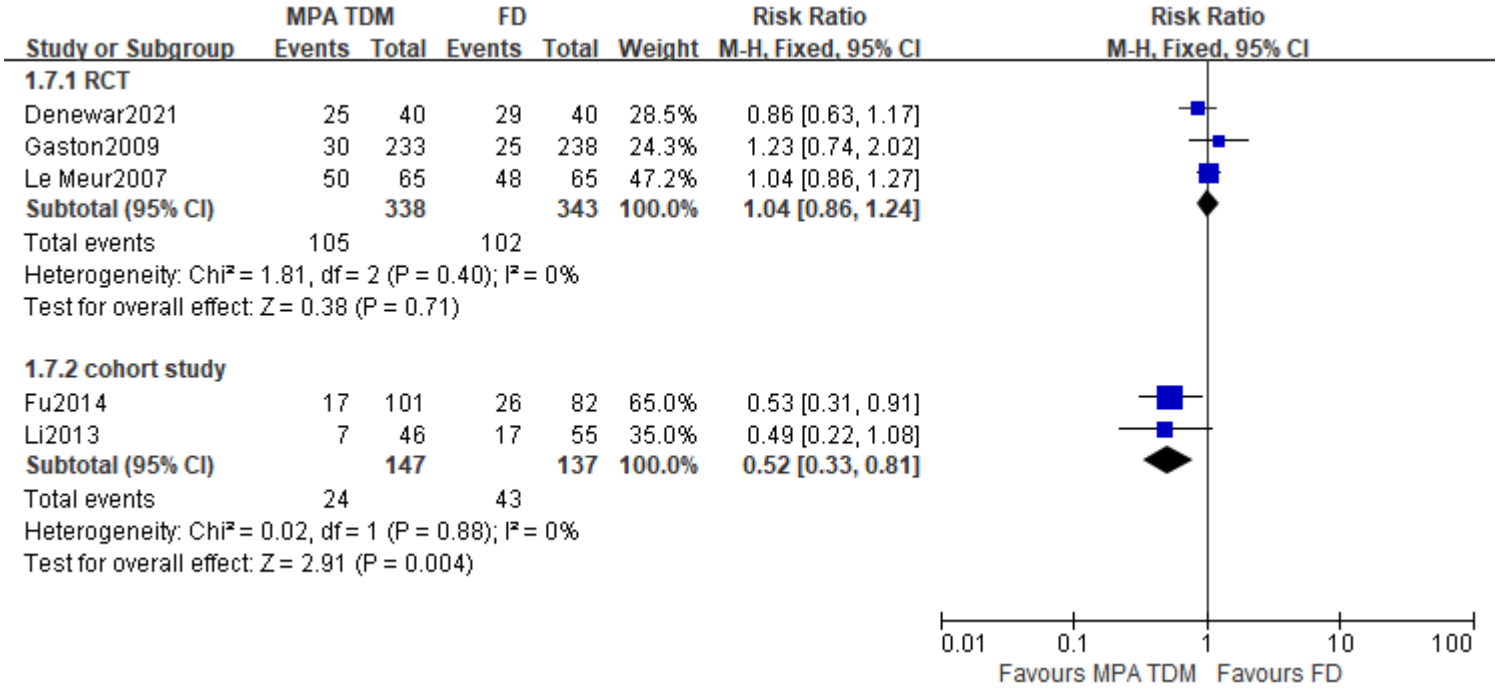
| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| 2 RCTs [5,8] | | | | | | | | | | ⊕⊕⊕○ |
| **Virus infection**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 5/101 | 7/82 | 0.58 [0.19, 1.76] | Very low<br>⊕○○○ |
| **Fungal infection**<br>1 RCT [5] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 9/91 | 8/92 | 1.14 [0.46, 2.82] | Moderate<br>⊕⊕⊕○ |
| **Fungal infection**<br>1 cohort study [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 1/101 | 2/82 | 0.41 [0.04, 4.40] | Very low<br>⊕○○○ |
| **Thrombocytopenia**<br>2 RCTs [3,8] | Not serious | Not serious | Not serious | Serious | Undetected | None | 25/489 | 33/492 | 0.76 [0.46, 1.26] | Moderate<br>⊕⊕⊕○ |
| **Thrombocytopenia**<br>1 cohort study [6] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 2/46 | 3/55 | 0.80 [0.14, 4.57] | Very low<br>⊕○○○ |
| **Malignancy**<br>1 RCT [1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 6/233 | 7/238 | 0.88 [0.30, 2.57] | Moderate<br>⊕⊕⊕○ |
| **GI AEs**<br>2 RCTs [2,8] | Not serious | Very serious | Not serious | Not serious | Undetected | None | 17/105 | 34/105 | 0.50 [0.29, 0.86] | Low<br>⊕⊕○○ |

RCTs, randomized controlled trials; AR, acute rejection; BPAR, biopsy-proven acute rejection; MMF, mycophenolate mofetil; GI, Gastrointestinal; AEs, adverse events

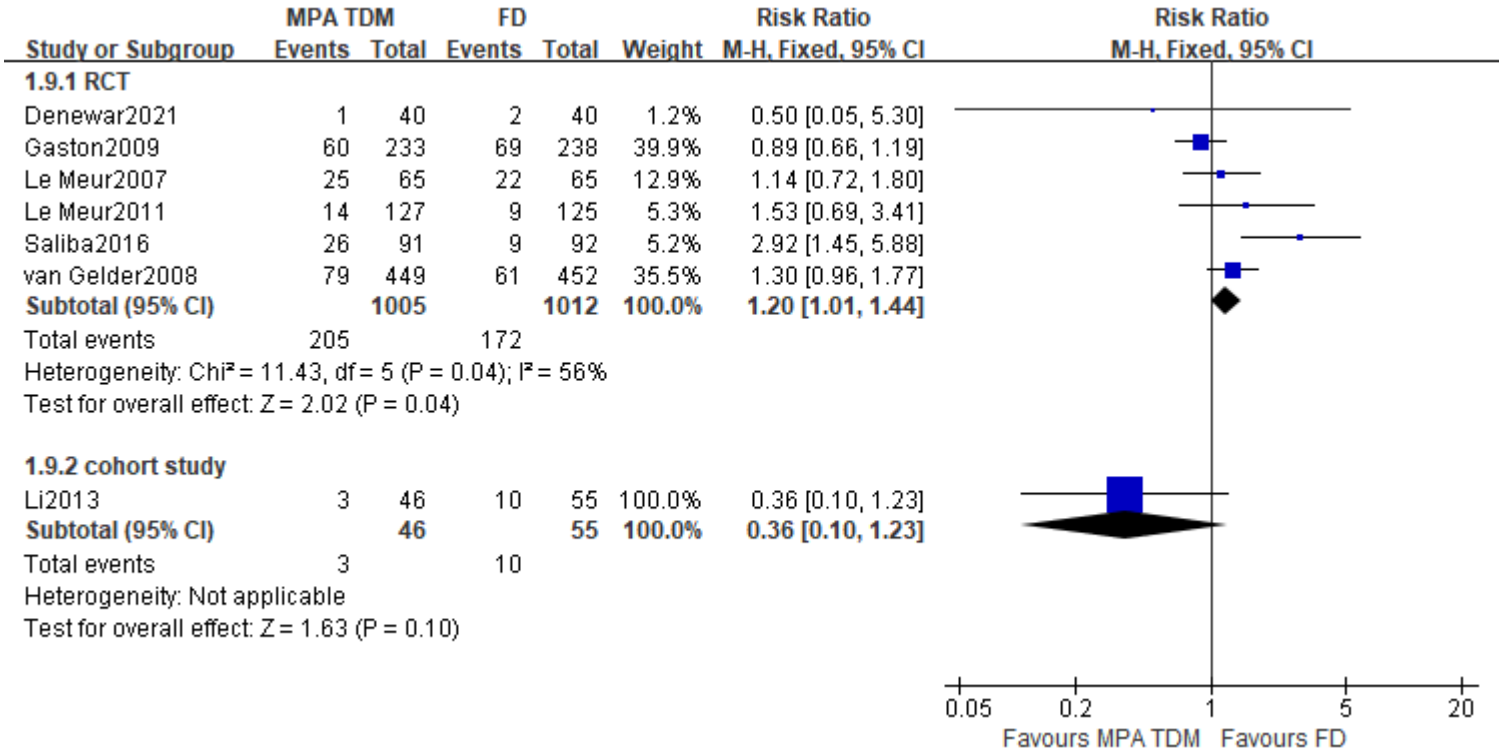
**Supplemental Figure 1: Acute rejection (AR) for MPA TDM vs fixed-dose (FD)**



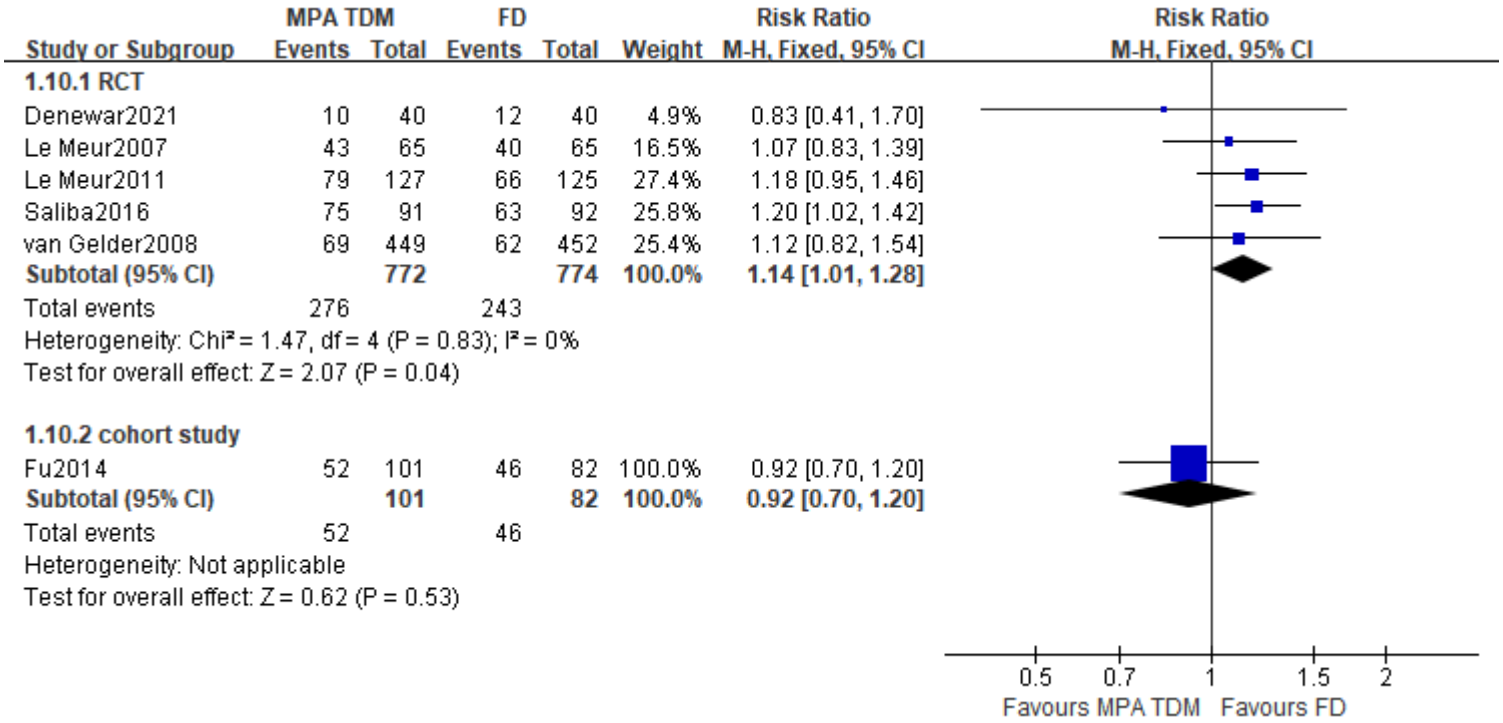
**Supplemental Figure 2: Infection for MPA TDM vs FD**



**Supplemental Figure 3: Leukopenia for MPA TDM vs FD**



**Supplemental Figure 4: Anemia for MPA TDM vs FD**




Qualitative analysis of 2 studies revealed that the TDM of MPA is particularly beneficial in patients in the early post-transplantation period and patients with reduced corticosteroid doses, and its benefits outweigh its risks in high-risk populations.

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## Recommendation 2

## Question 2*: What is the importance of using mycophenolic acid (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?

| Population | Intervention/Comparison | Outcomes |
|---|---|---|
| Solid organ transplantation recipients treated with MPA | $C_0$ vs AUC | Clinical efficacy and safety |

**Table1 The comparison of the correlation between $C_0$ and AUC**

| Studies (Author year) | Population | No. of patients | Outcome | Conclusion | Therapeutic range | Quality of evidence |
|---|---|---|---|---|---|---|
| Dosch 2006[1] | Heart transplant | 62 | The correlation between $C_0$ and total $AUC_{0\text{-}12h}$ $r^2$=0.36 (with CsA)<br>The correlation between $C_0$ and total $AUC_{0\text{-}12h}$ $r^2$=0.61 (with sirolimus)<br>The correlation between $C_0$ and total AUC $r^2$=0.75 | Abbreviated MPA AUC estimates predicted drug exposure more accurately than did MPA $C_0$ levels in the patients studied | NR | Moderate |
| Miura 2011[2] | Renal transplant | 86 | Day 28 after transplantation: $AUC_{0\text{-}12h} = 7.013C_0 + 37.14$, $r^2$=0.417<br>1 year after transplantation: $AUC_{0\text{-}12h} = 4.904C_0 + 38.24$, $r^2$=0.312 | To keep the MPA $AUC_{0\text{-}12h}$>30 mg•h/L, the plasma threshold for maintaining the MPA $C_0$ with tacrolimus should be set >2.0 mg/L | $C_0$>2.0 mg/L<br>$AUC_{0\text{-}12h}$ 30-60 mg•h/L | Moderate |
| Todorova 2015[3] | Pediatric renal transplant | 26 | $C_0$=0.07527 $AUC_{0\text{-}12h}$ - 1.042<br>r=0.7769, $r^2$=0.5075, p<0.0001 | MPA trough level monitoring may be a feasible monitoring option to improve patient exposure and possibly outcomes. | $AUC_{0\text{-}12h}$ 30-60 mg•h/L | Moderate |

CsA, cyclosporine A; NR, not reported.

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## Recommendations 3 and 4

## Question 4*: When is (MPA) plasma concentration first measured?

## Question 5*: What is (AUC) sampling time point and calculation method?

| Population | Intervention/Comparison | Outcomes |
|---|---|---|
| Solid organ transplantation recipients treated with MPA | The comparison of different $C_0$ sampling time points; the comparison of different AUC sampling time points (I: the most common time point, C: other time points) | Clinical efficacy, safety and pharmacokinetic/pharmacodynamic (PK/PD) parameters |

**Table 1 The distribution of sampling time points used for limited sampling strategies (LSS) of mycophenolate mofetil (MMF)**

| | $C_0$ | $C_{0.5}$ | $C_{0.67}$ | $C_1$ | $C_{1.5}$ | $C_2$ | $C_4$ | $C_6$ | $C_8$ |
|---|---|---|---|---|---|---|---|---|---|
| **Renal transplant** | √ | | √ | | | √ | | | |
| | | √ | | | | √ | √ | | |
| | | √ | | | | √ | | | √ |
| | √ | | √ | | | √ | | | |
| | | | | √ | | √ | √ | | √ |
| **Lung transplant** | √ | | | | √ | | | | |
| | √ | | | | | √ | | | |
| | | | | √ | | | √ | | √ |
| **Heart transplant** | | √ | | √ | | √ | | | |
| | | √ | | | | √ | √ | √ | |
| **Liver transplant** | | | | √ | | √ | | √ | √ |

√ means recommendation

## Table 2 The distribution of sampling time points used for LSS of enteric-coated mycophenolate sodium (EC-MPS)

| | $C_0$ | $C_{0.5}$ | $C_1$ | $C_{1.5}$ | $C_2$ | $C_3$ | $C_{3.5}$ | $C_4$ | $C_6$ | $C_8$ | $C_9$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Renal transplant** | | | | √ | | | √ | | | | |
| | | | √ | | √ | | | √ | | | |
| | | | | √ | | | | √ | √ | | |
| | | √ | √ | | √ | | | | | | |
| | | √ | | √ | √ | | | | | | |
| | √ | | √ | | √ | | | | | | |
| | √ | | √ | | | | | | | √ | |
| | √ | | | | | √ | | √ | | | |
| | | | √ | | | √ | | | | | √ |
| | | | √ | √ | √ | | | √ | | | |
| | | | √ | | √ | | | √ | √ | | |
| | √ | | | | | √ | | √ | | √ | |
| **Renal transplant and liver transplant** | | | √ | | √ | √ | | | √ | | |

√ means recommendation

## Table 3 LSS formulas of MMF

| Studies (Author year) | Population | Immunosuppression regimen (race) | LSS formula | Correlation $r^2$ | Establishment method |
|---|---|---|---|---|---|
| Van 2004[1] | Renal transplant | CsA and glucocorticoid (Netherlands, France) | $7.182 + 4.607 \times C_0 + 0.998 \times C_{0.67} + 2.149 \times C_2$ | Model development: 0.73<br>Model validation: 0.75 and 0.67 | MRA |
| Zhou 2007[2] | Renal transplant | CsA and glucocorticoid (China) | LSS1:$14.81 + 0.80 \times C_{0.5} + 1.56 \times C_2 + 4.80 \times C_4$<br>LSS2:$11.29 + 0.51 \times C_{0.5} + 2.13 \times C_2 + 8.15 \times C_8$ | LSS1: 0.70<br>LSS2: 0.88 | MRA |
| Musuamba 2009[3] | Renal transplant | CsA or sirolimus and glucocorticoid (Belguim) | $8.64 + 5.13 \times C_0 + 0.62 \times C_{0.66} + 2.84 \times C_2$ | 0.79 | MRA |

| | | | | | |
|---|---|---|---|---|---|
| Zhang 2018[4] | Renal transplant | Tac and glucocorticoid (China) | $8.36 + 7.49 \times C_8 + 1.34 \times C_2 + 1.66 \times C_4 + 0.76 \times C_1$ | 0.948 | MRA |
| Ting 2006[5] | Lung transplant | CsA or Tac and glucocorticoid (Canada) | LSS1: $\log AUC = 0.241 \times \log C_0 + 0.406 \times \log C_2 + 1.140$<br>LSS2: $\log AUC = 0.202 \times \log C_0 + 0.411 \times \log C_{1.5} + 1.09$ | LSS1: 0.828<br>LSS2: 0.791 | MRA |
| Tanaka 2019[6] | Lung transplant | Tac (Japan) | $4.04 + 1.64 \times C_1 + 3.08 \times C_4 + 5.17 \times C_8$ | 0.923 | MRA |
| Pawinski 2009[7] | Heart transplant | CsA and glucocorticoid (Poland) | $9.69 + 0.63 \times C_{0.5} + 0.61 \times C_1 + 2.20 \times C_2$ | 0.841 | MRA |
| Xiang 2021[8] | Heart transplant | Tac and glucocorticoid (China) | $8.424 + 0.781 \times C_{0.5} + 1.263 \times C_2 + 1.660 \times C_4 + 3.022 \times C_6$ | Model development: 0.844<br>Model validation: 0.803 (dispersible tablets) 0.800 (capsules) | MRA |
| Yu 2007[9] | Liver transplant | Tac (China) | $6.03 + 0.89 \times C_1 + 1.94 \times C_2 + 2.24 \times C_6 + 4.64 \times C_8$ | 0.911 | MRA |

CsA, cyclosporine A; MRA, multiple regression analysis; Tac, tacrolimus.

## Table 4 LSS formulas of EC-MPS

| Studies (Author year) | Population | Immunosuppression regimen (race) | LSS formula | Correlation $r^2$ | Establishment method |
|---|---|---|---|---|---|
| Fructuoso 2012[10] | Renal transplant | Tac and glucocorticoid (White) | LSS1: $15.99 + 0.87 \times C_1 + 0.68 \times C_2 + 7.85 \times C_4$<br>LSS2: $11.15 + 0.68 \times C_1 + 0.45 \times C_{1.5} + 0.57 \times C_2 + 8.16 \times C_4$ | Model development: LSS1: 0.843; LSS2: 0.888<br>Model validation: LSS1: 0.714; LSS2: 0.760 | MRA |
| Yao 2015[11] | Renal transplant | Tac and glucocorticoid (China) | LSS1: $15.09 + 1.05 \times C_{1.5} + 1.8 \times C_4 + 4.18 \times C_6$<br>LSS2: $10.44 + 0.7 \times C_1 + 1.22 \times C_2 + 1.75 \times C_4 + 4.36 \times C_6$ | LSS1: 0.902<br>LSS2: 0.941 | MRA |
| de Winter 2009[12] | Renal transplant | With or without CsA (Netherlands) | LSS1: $36.536 + 1.642 \times C_{0.5} + 0.569 \times C_{1.5} + 0.905 \times C_2$ (with CsA)<br>LSS2: $19.801 + 1.827 \times C_{0.5} + 1.111 \times C_1 + 1.429 \times C_2$ (without CsA) | Model development: LSS1: 0.42; LSS2: 0.69<br>Model validation: LSS1: 0.33; LSS2: 0.31 | MRA |
| Capone 2011[13] | Renal transplant | CsA (Italy) | LSS1: $22.906 + 3.88 \times C_0 + 1.117 \times C_1 + 7.527 \times C_8$<br>LSS2: $35.064 + 3.784 \times C_0 + 1.002 \times C_1 + 1.192 \times C_2$ | LSS1: 0.901<br>LSS2: 0.846 | MRA |
| Jia 2017[14] | Renal transplant | Tac (China) | LSS1: $6.629 + 8.029 \times C_0 + 0.592 \times C_3 + 1.786 \times C_4$ | Model development: LSS1: 0.910; LSS2: 0.959<br>Model validation: LSS1: 0.573; LSS2: 0.873 | MRA |

| | | | | | |
|---|---|---|---|---|---|
| | | | LSS2: 3.132 + 5.337 × $C_0$ + 0.735 × $C_3$ + 1.783 × $C_4$ + 3.065 × $C_8$ | | |
| Musuamba 2013[15] | Renal transplant | Tac and glucocorticoid (Belguim) | 16.5 + 4.9 × $C_{1.5}$ + 6.7 × $C_{3.5}$ | Model development: 0.82(MRA); 0.90 (Bayesian)<br>Model validation: 0.66 (MRA); 0.75 (Bayesian) | MRA and Bayesian estimators |
| Pawinski 2013[16] | Renal transplant, liver transplant | CsA and glucocorticoid (Poland) | LSS1: 17.28 + 0.89 × $C_1$ + 1.76 × $C_3$ + 6.09 × $C_9$<br>LSS2: 8.53 + 1.09 × $C_1$ + 1.07 × $C_2$ + 1.65 × $C_3$ + 3.59 × $C_6$ | LSS1: 0.824<br>LSS2: 0.898 | MRA |

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## Recommendations 5 and 6

## Question 6*: What is the therapeutic range of mycophenolic acid (MPA) monitoring indicators?

| Population | Intervention/Comparison | Outcomes |
|---|---|---|
| Solid organ transplantation recipients treated with MPA | Area under curve (AUC) 30-60 mg•h/L vs other therapeutic range; $C_0$ 1-3.5 mg/L vs other therapeutic range | Clinical efficacy, safety and pharmacokinetic/pharmacodynamic (PK/PD) parameters |

**Table 1 The comparison of therapeutic range of AUC**

| Studies (Author year) | Population | Number of patients | Groups | Combined medications | Clinical outcomes | Conclusion | Therapeutic range | Detection methods | Quality of evidence |
|---|---|---|---|---|---|---|---|---|---|
| Gelder 1999[1] 1 RCT | Renal transplant | 150 | AUC 16.1 mg•h/L vs AUC 32.2 mg•h/L vs AUC 60.6 mg•h/L | CsA | BPAR: the incidence in the low target AUC was high compared to intermediate/high group (*P*=0.043). | This study has demonstrated a highly statistically significant relationship between median MPA AUC and the risk of rejection | NR | HPLC | Moderate |
| Gelder 2008[2] 1 RCT | Renal transplant | 825 | AUC<30 mg•h/L Vs AUC>30 mg•h/L | CsA or Tac | The risk of developing a BPAR in the first year posttransplant in patients with a day3 MPA AUC of less than 30 mg•h/L was higher than those with a corresponding value of more than 30 mg•h/L (*P*=0.018) | Initial MMF doses underexpose early after transplantation, increasing the risk for BPAR | AUC 30-60 mg•h/L | HPLC or EMIT | Moderate |
| Kuypers 2008[3] Jiang 2015[4] Liu 2016[5] 3 cohort studies | Renal transplant | 738 | AUC<30 mg•h/L vs AUC 30-60 mg•h/L vs AUC>60 mg•h/L | 2studies[3,5]: Tac 1study[4]: CsA or Tac | ① Significantly more episodes of leukopenia were associated with AUC>60 mg•h/L (*P*=0.03). Anemia was also significantly associated with higher MPA exposure ranges (*P*=0.004 for hemoglobin<12 g/dL; P=0.03 for hemoglobin<10 g/dL). | Renal allograft recipients suffering from leukopenia or anemia related to MMF could potentially benefit, at least in part, from MMF dose adjustments based on target therapeutic MPA AUC ranges between 30 and 60 mg•h/L. | AUC 30-60 mg•h/L | EMIT[3,5] LC/MS[4] | Low |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | ②Incidence of herpes zoster was significantly different among three groups (*P*=0.014).<br>③There was no significant difference between 30-60 mg•h/L group and >60 mg•h/L group in the incidence of gastrointestinal, haematological, infectious and malignant AEs (*P*>0.05).<br>④There was no significant difference in the incidence of elevated transaminase, diarrhea, respiratory infection and urinary infection (*P*>0.05). | The incidence of AEs was relatively low and no significant relationship with pharmacokinetic parameters was found in our study.<br>MPA exposure within the therapeutic range may effectively reduce the occurrence of herpes zoster, but the incidence of drug-induced liver damage, diarrhea, and infection (respiratory system, Urinary system) in different ranges has no significant difference, suggesting that this therapeutic range cannot effectively control such adverse events | | | |
| Hiroshi 2020[6]<br>1 cohort study | Lung transplant | 59 | AUC<22.73 mg•h/L vs AUC 22.73-40.46 mg•h/L vs AUC>40.46 mg•h/L | Tac | The cumulative occurrence rates of the adverse events (CLAD and infections) in adequate group were significantly lower than inadequate group (P = 0.005). | MMF intake dose adjustment by MPA AUC may improve the clinical outcomes after lung transplantations. | AUC 22.73 -40.46 mg•h/L | LC/ MS | Moderate |

RCT, randomized controlled trial; CsA, cyclosporine A; BPAR, biopsy-proven acute rejection; NR, not reported; HPLC, high performance liquid chromatography; Tac, tacrolimus; MMF, mycophenolate mofetil; EMIT, enzyme multiplied immunoassay technique; AEs, adverse events; LC/MS, liquid chromatography mass spectrometry; CLAD, chronic lung allograft dysfunction.

## Table 2 The comparison of therapeutic range of $C_0$

| Studies (Author year) | Population | Number of patients | Groups | Combined medications | Clinical outcomes | Conclusion | Therapeutic ranges | Detection methods | Quality of evidence |
|---|---|---|---|---|---|---|---|---|---|
| Jung 2020[7]<br>1 cohort study | Renal transplant | 79 | $C_0$<3.5 mg/L vs $C_0$≥3.5 mg/L | Tac | Leukopenia (*P*=0.041) and anemia (*P*=0.003) occurred more frequently in patients with MPA levels of ≥3.5 mg/L compared with those with MPA levels of <3.5 mg/L. | In conclusion, MPA $C_0$ below approximately 3.5 mg/L reduces the risk of hematologic side effects. | $C_0$<3.5 mg/L | PETINIA | Low |
| Yamani 2000[8]<br>1 cohort study | Heart transplant | 215 | $C_0$<2 mg/L vs $C_0$≥2 mg/L | CsA or Tac | When MMF trough level of 2 mg/L or greater was used as the cutoff point, the incidence of rejection decreased significantly both within 6 months of transplant and 6-12 months after the transplant (both *P*=0.05). | Monitoring of MMF trough levels may play a role in the management of acute rejection in cardiac transplant recipients during the first-year after the transplant. | $C_0$ 2-4 mg/L | EMIT | Low |

PETINIA, particle-enhanced turbidimetric inhibition immunoassay.

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## Recommendation 7

## Question 7*: What is the frequency of mycophenolic acid (MPA) blood level monitoring?

| Population | Intervention/Comparison | Outcomes |
|---|---|---|
| Solid organ transplantation recipients treated with MPA | Different monitoring frequency<br>(I: the most common monitoring frequency, C: other monitoring frequency) | Clinical efficacy, safety and pharmacokinetic/pharmacodynamic (PK/PD) parameters |

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## Recommendation 8

## Question 8*: What method should be used to implement mycophenolic acid (MPA) therapeutic drug monitoring (TDM)?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Solid organ transplant recipients treated with MPA | Chromatography | Immunoassay | Precision, accuracy, linearity, sensitivity, limit of detection, etc. |

Chromatography can be performed with small sample volumes and shows prominent advantages. However, (LC–MS) technology is demanding, and the pre-treatment process is cumbersome, with limitations such as matrix effects. Immunoassay is relatively fast, has simple equipment requirements, and is commonly used clinically. However, it lacks specificity, is unstable, has a narrow linear range, and requires dilution, which may produce unreliable results.

**Table 1 HPLC vs EMIT consistency**

| No. | Studies | Linear relationship | Linearity range | LLOQ | CV, precision, accuracy |
|---|---|---|---|---|---|
| 1 | Hosotsubo 2001[1] | EMIT=1.091×HPLC-0.089, $r^2$=0.990;<br>EMIT=1.069×HPLC-0.133, $r^2$=0.990 (with Tac);<br>EMIT=1.122×HPLC+0.164, $r^2$=0.994 (with CsA)<br>EMIT=1.0204 ×HPLC + 0.0201; | EMIT: 0.01-15.0 μg/ml | EMIT: 0.01 μg/mL | Intra-assay CV: 1.58%-3.68%<br>Inter-assay CV: 1.23%-7.57% |
| 3 | Blanchet 2008[2] | EMIT=1.064 ×HPLC-0.1509<br>(Severe renal impairment);<br>EMIT=1.019×HPLC +0.0326 (with CsA);<br>EMIT=1.0635×HPLC-0.2898 (with Tac) | HPLC: 0.5-20 mg/L<br>EMIT: 0.5-15 mg/L | HPLC: 0.5 mg/L | HPLC: 2.4%-8.9%<br>EMIT: 3.1%-6.6% |

| | | | | | |
|---|---|---|---|---|---|
| 4 | Lian 2017[3] | EMIT=1.1082HPLC+0.3812, $r^2$=0.983 (0-15 mg/L);<br>EMIT=0.9894HPLC+2.2438, $r^2$=0.9698 (>15 mg/L) | HPLC: 0.1-20 mg/L<br>EMIT: 0.1-15 mg/L | HPLC: 0.1 mg/L<br>EMIT: 0.1 mg/L | HPLC intraday and interday RSD < 10%<br>EMIT intraday and interday RSD < 20% |
| 5 | Beal 1998[4] | HPLC=-1.43+0.907×EMIT ($r^2$=0.923) | HPLC: 0.5-50 mg/L<br>EMIT: 0.0-15.0 mg/L | HPLC: 0.2 mg/L<br>EMIT: 0.5 mg/L | EMIT: 8.9%, 4.6%, 3.6% (at low, medium and high concentration ranges, respectively)<br>HPLC: 11.8%, 2.1%, 1.4% (quality controls at 0.8 mg/L, 25 mg/L, and 40 mg/L) |
| 6 | Westley 2005[5] | EMIT=0.973×HPLC+0.55 ($r^2$=0.851) | 0-20 mg/L MPA<br>0-200 mg/L MPAGe<br>0-100 mg/L MPAGa | HPLC: MPA 0.25 mg/L, MPAGe 0.5 mg/L, MPAGa 0.25 mg/L | MPA, MPAGa, MPAGe intra-assay and inter-assay CV: 0.9%-18.9% |
| 7 | Yeung 1999[6] | EMIT=1.080×HPLC+0.276 (r=0.99) | HPLC: 0.2-40.0μg/mL | HPLC: 0.2 μg/mL | CV≤8%<br>CV 7.9% -9.5% |
| 8 | Vogl 1999[7] | EMIT= 1.012×HPLC + 0.244 (r=0.970) | NR | EMIT: 0.20 mg/L | EMIT: with-run imprecision 2.5% - 4.4%, between-day imprecision 7.9%-10.8%<br>HPLC: with-run imprecision 1.3%-4.9%, between-day imprecision 4.7%-12.1% |
| 9 | Kunicki 2015[8] | PETINIA = 1.100×HPLC + 0.38($r^2$= 0.9230，P<0.0001)<br>EMIT = 1.300×HPLC + 0.24 ($r^2$= 0.9702，P<0.0001) | HPLC:0.1-30 μg/mL<br>PETINIA :0.2-30 μg/mL<br>EMIT:0.1-15 μg/mL | HPLC:0.1 μg/mL | Intraday precision:1.4%-9.3%<br>Interday precision: 2.9%-5.8%<br>Imprecision < 10% |

HPLC, high-performance liquid chromatography; EMIT, enzyme multiplied immunoassay technique; LLOQ, lower limit of quantitation; CV, coefficients of variation; Tac, tacrolimus; CsA, cyclosporine A; RSD, relative standard deviation; MPAG, MPA glucuronide; MPAGe, mycophenolate ether glucuronide; MPAGa, mycophenolate acyl glucuronide; NR, not reported.

## Table 2 HPLC vs CEDIA consistency

| No. | Studies (Author year) | Linear relationship | Linearity range | LLLQ | CV, precision, accuracy |
|---|---|---|---|---|---|
| 1 | Dasgupta 2013[9] | CEDIA = 1.1558x + 0.2876, r = 0.97;<br>CEDIA = 1.1181× HPLC-UV+ 0.2745, r=0.98 (renal transplant);<br>CEDIA = 1.3337× HPLC-UV + 0.1493, r=0.94 (liver transplant); | HPLC: 0.2-40 ug/ml<br>CEDIA: 0.3-10 ug/ml | CEDIA: 10 μg/mL | CEDIA: within-run precision 9.3%, between run precision 13.3% (Low control)<br>CEDIA: within-run precision 1.5%，between run precision4.9% (high control) |
| 2 | Shipkova 2010[10] | CEDIA=1.176×HPLC-UV + 0.191 (r=0.922) | HPLC: MPA 50 mg/L, AcMPAG 10 mg/L, MPAG 500 mg/L, MMF 100 mg/L;<br>CEDIA: MPA 10 mg/L | HPLC: MPA 0.05 mg/L, AcMPAG 0.1 mg/L, MPAG 1 mg/L<br>CEDIA: MPA 0.3 mg/L | HPLC: 0.6%-2.75% |
| 3 | Westley 2006[11] | CEDIA=1.18 ×HPLC-UV+0.45 ($r^2$=0.83) | CEDIA: 0-10 mg/L | NR | CEDIA:<br>Within run CV < 5%<br>Between run CV< 7% |

CEDIA, cloned enzyme donor immunoassay; HPLC-UV, High-performance liquid chromatography-ultraviolet; MMF, mycophenolate mofetil, NR, not reported; AcMPAG, acyl-glucuronide MPA.

## Table 3 LC-MS/MS vs EMIT/PETINIA consistency

| No. | Studies (Author year) | Linear relationship | Linearity range | LLLQ | CV, precision, accuracy |
|---|---|---|---|---|---|
| 1 | Brown 2010[12] | EMIT = 1.026×LC-MS/MS+0.181 ($r^2$=0.947) | LC-MS/MS: 2.5-50 mg/L | LC-MS/MS: 0.2 mg/L | LC-MS/MS: intra-assay precision 4.5%-19.33% |
| 2 | Premaud 2004[13] | EMIT= 1.094+1.094×LC-MS/MS ($r^2$=0.894) | LC-MS/MS:<br>MPA 0.1-30 mg/L<br>MPAG 1-300 mg/L | MPA: 0.1 mg/L<br>MPAG: 1 mg/L | LC-MS/MS:<br>MPA: within day 4.96%-12.28%; between day 1.17%-6.89%<br>MPAG: within day 3.66%-13.37%; between day 2.24%-8.90%<br>EMIT:<br>MPA: within day 1.62%-4.83%; between day CV3.97%-7.42% |
| 3 | Kikuchi 2018[14] | PETINIA=1.104×LC-MS/MS+0.229 ($r^2$=0.969) | PETINIA: 0.2-30.0 μg/mL<br>LC-MS/MS: 0.06-20.0 μg/mL | The lowest concentration with a signal-to-noise ratio of at least 10 | Intra-day and inter-day < 3.7%<br>Accuracy±8.5% |
| 4 | Liu 2020[15] | LC-MS/MS= 0. 744×EMIT-0. 40 ($r^2$=0.963) | LC-MS/MS: 0. 025-20 μg/mL<br>EMIT: 0.16-24. 87 μg/mL | LC-MS/MS: 0.047 μg/mL | LC-MS/MS: RSD 9.42% |

LC-MS/MS, Liquid chromatography-tandem mass spectrometry; PETINIA, particle enhanced turbidimetric inhibition immunoassay.

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## Recommendation 9

## Question 9*: Which formulation is preferred, (MMF) or (EC-MPS)?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Solid organ transplant recipients treated with mycophenolate acid (MPA) | MMF | EC-MPS | Clinical efficacy and safety |

**Table 1 Comparison of efficacy and safety between MMF and EC-MPS**

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **Efficacy failure**<br>2 RCTs [1,2] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 60/372 | 69/373 | 0.86 [0.64, 1.16] | High<br>⊕⊕⊕⊕ |
| **AR**<br>6 RCTs [1-6] | Very serious | Not serious | Not serious | Not serious | Undetected | None | 27/559 | 53/571 | 0.60 [0.28, 1.28] | Low<br>⊕⊕○○ |
| **AR**<br>1 observational study [6] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 1/44 | 4/62 | 0.35 [0.04, 3.05] | Very low<br>⊕○○○ |
| **BPAR**<br>4 RCTs [1,2,4,7] | Serious | Not serious | Not serious | Not serious | Undetected | None | 70/497 | 77/499 | 0.90 [0.68, 1.21] | Moderate<br>⊕⊕⊕○ |
| **BPAR**<br>1 observational study [8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 1/191 | 5/183 | 0.19 [0.02, 1.62] | Low<br>⊕⊕○○ |
| **Graft loss**<br>4 RCTs [1-4] | Serious | Not serious | Not serious | Not serious | Undetected | None | 13/434 | 19/444 | 0.68 [0.34, 1.35] | Moderate<br>⊕⊕⊕○ |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **MPA discontinuation**<br>6 RCTs [1-3,5,7,9] | Serious | Not serious | Not serious | Serious | Undetected | None | 78/708 | 89/717 | 0.88 [0.67, 1.17] | Low<br>⊕⊕○○ |
| **MPA discontinuation**<br>1 observational study [8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 2/193 | 5/186 | 0.39 [0.08, 1.96] | Low<br>⊕⊕○○ |
| **Death**<br>4 RCTs [1,2,4,7] | Serious | Not serious | Not serious | Not serious | Undetected | None | 6/497 | 11/499 | 0.55 [0.20, 1.47] | Moderate<br>⊕⊕⊕○ |
| **Death**<br>2 observational studies [6,8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 0/237 | 1/248 | 0.47[0.02, 1.20] | Low<br>⊕⊕○○ |
| **Overall AEs**<br>2 RCTs [1,2] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 358/372 | 357/373 | 1.01 [0.98, 1.03] | High<br>⊕⊕⊕⊕ |
| **Overall infections**<br>4 RCTs [1,2,4,7] | Serious | Not serious | Not serious | Not serious | Undetected | None | 290/497 | 298/499 | 0.98 [0.88, 1.08] | Moderate<br>⊕⊕⊕○ |
| **Overall infections**<br>1 observational study [8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 121/193 | 70/186 | 1.67 [1.34, 2.06] | Low<br>⊕⊕○○ |
| **Serious infections**<br>2 RCTs [1,2] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 33/372 | 52/373 | 0.64 [0.42, 0.96] | High<br>⊕⊕⊕⊕ |
| **CMV infection**<br>3 RCTs [1,2,7] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 50/447 | 48/448 | 1.03 [0.72, 1.47] | High<br>⊕⊕⊕⊕ |
| **CMV infection**<br>1 observational study [8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 13/193 | 7/186 | 1.79 [0.73, 4.39] | Low<br>⊕⊕○○ |
| **CMV disease**<br>1 RCT [2] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 10/213 | 9/210 | 1.10 [0.45, 2.64] | High<br>⊕⊕⊕⊕ |
| **BK infection** | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 6/193 | 0/186 | 12.53 [0.71, 220.88] | Low |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| 1 observational study [8] | | | | | | | | | | ⊕⊕○○ |
| **Urinary tract infection**<br>2 RCTs [4,7] | Serious | Not serious | Not serious | Serious | Undetected | None | 22/125 | 25/126 | 0.89 [0.53, 1.49] | Low<br>⊕⊕○○ |
| **Urinary tract infection**<br>1 observational study [8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 33/193 | 13/186 | 2.45 [1.33, 4.50] | Low<br>⊕⊕○○ |
| **Total GI AEs**<br>5 RCTs [1,2,4,7,9] | Serious | Not serious | Not serious | Not serious | Undetected | None | 347/696 | 354/696 | 0.98 [0.89, 1.07] | Moderate<br>⊕⊕⊕○ |
| **Total GI AEs**<br>2 observational studies [6,8] | Not serious | Serious | Not serious | Not serious | Undetected | None | 104/237 | 100/250 | 1.03 [0.85, 1.26] | Moderate<br>⊕⊕⊕○ |
| **Diarrhea**<br>4 RCTs [1,4,7,9] | Serious | Not serious | Not serious | Not serious | Undetected | None | 63/483 | 66/486 | 0.96 [0.70, 1.30] | Moderate<br>⊕⊕⊕○ |
| **Diarrhea**<br>1 observational study [8] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 65/193 | 42/193 | 1.55 [1.11, 2.16] | Low<br>⊕⊕○○ |
| **Nausea**<br>3 RCTs [1,4,9] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 20/358 | 32/360 | 0.84 [0.57, 1.23] | High<br>⊕⊕⊕⊕ |
| **Nausea**<br>3 RCTs [1,4,9] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 9/358 | 17/360 | 1.04 [0.64, 1.67] | High<br>⊕⊕⊕⊕ |
| **Dyspepsia**<br>2 RCTs [1,9] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 25/358 | 23/360 | 1.09 [0.63, 1.87] | High<br>⊕⊕⊕⊕ |
| **Malignancy**<br>2 RCTs [2,4] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 6/288 | 6/285 | 0.99 [0.32, 3.03] | High<br>⊕⊕⊕⊕ |
| **Overall Hematologic AEs**<br>1 RCT [9] | Not serious | Not applicable | Not serious | Not serious | Undetected | None | 5/199 | 8/197 | 0.62 [0.21, 1.86] | High<br>⊕⊕⊕⊕ |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **Leukopenia**<br>1 RCT [5] | Serious | Not applicable | Not serious | Serious | Undetected | None | 1/50 | 3/51 | 0.34 [0.04, 3.16] | Low<br>⊕⊕○○ |
| **Neutropenia**<br>2 RCTs [1,2] | Not serious | Not serious | Not serious | Not serious | Undetected | None | 2/372 | 6/373 | 0.34 [0.07, 1.67] | High<br>⊕⊕⊕⊕ |

AR, acute rejection; BPAR, biopsy-proven acute graft rejection; AE, adverse event; CMV, Cytomegalovirus; BK, BK polyomavirus; GI, gastrointestinal tract.

## Supplemental Figure 1 EC-MPS vs MMF Incidence of serious infections


In liver transplant recipients, 2 RCTs showed that by 12 weeks post-transplant, EC-MPS significantly improved gastrointestinal adverse reactions, including reflux, dyspepsia, diarrhea, and constipation, with better tolerability and equivalent efficacy.

In heart transplant recipients, 1 study showed that EC-MPS and MMF had comparable efficacy, safety, and tolerability in the first year after heart transplant.

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## Recommendation 10

## Question 10*: What is the recommended initial dose for (MMF)?

| Population | Intervention | Comparison | Outcomes | Study design |
|---|---|---|---|---|
| Solid organ transplantation recipients treated with MMF | Intensified dose (ID) [1.5g twice a day (bid)] or low dose (LD) [1g once a day (qd) or 1.5g qd] | Standard dose (SD) (1g bid) | Clinical efficacy and safety | Randomized controlled trial (RCT) and cohort study |

**Table 1 The comparison between ID and SD of MMF**

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR ) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **Treatment failure**<br>2 RCTs [1,2] | Not serious | Serious | Not serious | Serious | Undetected | None | 132/324 | 133/338 | 1.04 [0.86, 1.25] | Low<br>⊕⊕○○ |
| **Rejection**<br>3 RCTs [1,3,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 81/398 | 107/405 | 0.78 [0.60, 1.00] | Moderate<br>⊕⊕⊕○ |
| **BPAR**<br>3 RCTs [1,2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 55/392 | 79/405 | 0.72 [0.53, 0.99] | Moderate<br>⊕⊕⊕○ |
| **Graft loss**<br>2 RCTs [1,2] | Not serious | Serious | Not serious | Serious | Undetected | None | 13/324 | 14/338 | 0.97 [0.46, 2.02] | Low<br>⊕⊕○○ |
| **MPA discontinuation**<br>1 RCT [1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 25/164 | 34/173 | 0.78 [0.48, 1.24] | Moderate<br>⊕⊕⊕○ |
| **Death**<br>2 RCTs [1,2] | Not serious | Not serious | Not serious | Serious | Undetected | None | 7/324 | 5/338 | 1.45 [0.47, 4.52] | Moderate<br>⊕⊕⊕○ |
| **Overall AEs**<br>1 RCT [3] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 16/166 | 7/165 | 2.27 [0.96, 5.38] | Moderate<br>⊕⊕⊕○ |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR ) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **Overall infection**<br>2 RCTs [1,2] | Not serious | Not serious | Not serious | Serious | Undetected | None | 130/324 | 142/336 | 0.95 [0.79, 1.14] | Moderate<br>⊕⊕⊕○ |
| **Overall hematological AEs**<br>1 RCT [2] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 38/160 | 42/165 | 0.93 [0.64, 1.37] | Moderate<br>⊕⊕⊕○ |
| **Overall GI AEs**<br>1 RCT [2] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 84/160 | 75/165 | 1.16 [0.92, 1.44] | Moderate<br>⊕⊕⊕○ |
| **CMV infection**<br>1 RCT [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 1/68 | 6/67 | 0.16 [0.02, 1.33] | Moderate<br>⊕⊕⊕○ |
| **Urinary tract infection**<br>1 RCT [4] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 11/68 | 17/67 | 0.64 [0.32, 1.26] | Moderate<br>⊕⊕⊕○ |
| **Anemia**<br>3 RCTs [1,2,4] | Not serious | Serious | Not serious | Serious | Undetected | None | 55/392 | 59/403 | 0.94 [0.69, 1.30] | Low<br>⊕⊕○○ |
| **Leucopenia**<br>3 RCTs [1,2,4] | Not serious | Serious | Not serious | Serious | Undetected | None | 89/392 | 65/403 | 1.41 [1.06, 1.87] | Low<br>⊕⊕○○ |
| **Thrombocytopenia**<br>3 RCTs [1,2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 15/392 | 24/403 | 0.65 [0.34, 1.21] | Moderate<br>⊕⊕⊕○ |
| **Diarrhea**<br>3 RCTs [1,2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 111/392 | 97/403 | 1.17 [0.93, 1.47] | Moderate<br>⊕⊕⊕○ |
| **Nausea**<br>3 RCTs [1,2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 77/392 | 64/403 | 1.22 [0.93, 1.61] | Moderate<br>⊕⊕⊕○ |
| **Vomiting**<br>3 RCTs [1,2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 47/392 | 44/403 | 1.09 [0.75, 1.58] | Moderate<br>⊕⊕⊕○ |

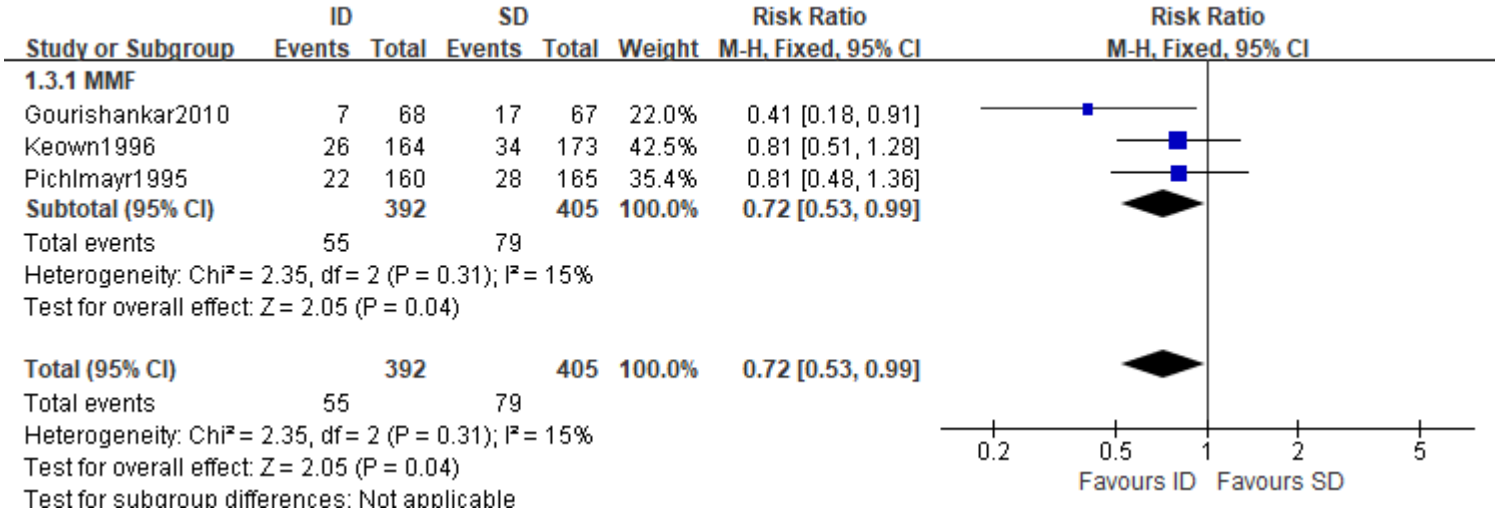
BPAR, biopsy-proven acute rejection; MPA, mycophenolic acid; AE, adverse event; GI, gastrointestinal; CMV, cytomegalovirus.

## Table 2 The comparison between LD and SD of MMF

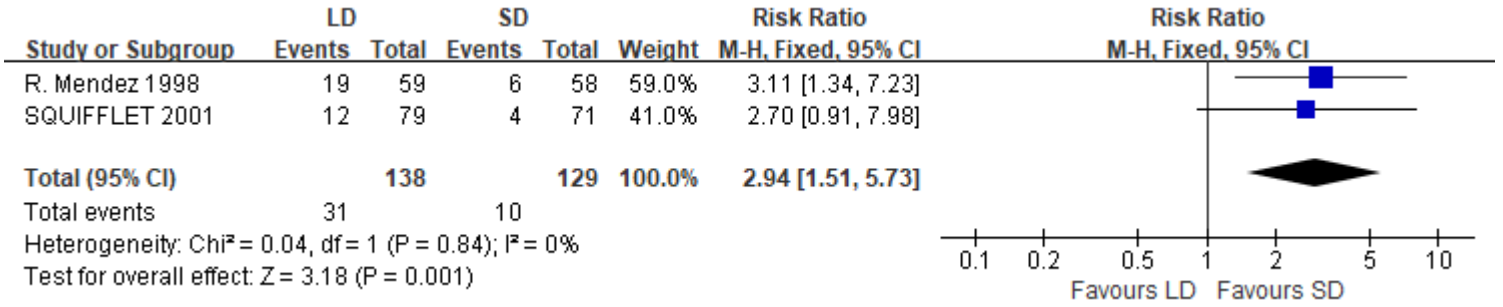
| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **BPAR**<br>2 RCTs[5,6] | Serious | Not serious | Not serious | Not serious | Undetected | None | 31/138 | 10/129 | 2.94 [1.51, 5.73] | Moderate<br>⊕⊕⊕○ |
| **MPA discontinuation**<br>2 RCTs[5,6] | Serious | Not serious | Not serious | Serious | Undetected | None | 19/138 | 15/129 | 1.19 [0.63, 2.25] | Low<br>⊕⊕○○ |
| **Death**<br>2 RCTs[5,6] | Serious | Not serious | Not serious | Serious | Undetected | None | 4/138 | 4/129 | 0.94 [0.24, 3.68] | Low<br>⊕⊕○○ |
| **Death**<br>3 cohort studies[7,8,9] | Not serious | Serious | Not serious | Serious | Undetected | None | 4/234 | 12/254 | 0.44 [0.18, 1.07] | Very low<br>⊕○○○ |
| **Graft loss**<br>2 cohort studies[8,9] | Not serious | Serious | Not serious | Not serious | Undetected | None | 5/134 | 15/94 | 0.25 [0.10, 0.62] | Very low<br>⊕○○○ |

MPA, mycophenolic acid.

**Supplemental Figure 1: Biopsy-proven acute rejection (BPAR) for ID vs SD**



## Supplemental Figure 2: BPAR for LD vs SD




## Supplemental Figure 3: Graft loss for LD vs SD

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## Recommendation 11

## Question 11*: What is the recommended initial dose for (EC-MPS)?

| Population | Intervention | Comparison | Outcomes | Study design |
|---|---|---|---|---|
| Renal transplant recipients treated with EC-MPS | Intensified dose (ID) (2880 mg/d for postoperative days 0-14, 2160 mg/d for postoperative days 15-42, and 1440 mg/d thereafter) or low dose (LD) (1080 mg/d) | Standard dose (SD) (1440 mg/d for days 0-30, 1260 mg/d for days 31-60, and 1080 mg/d thereafter) | Clinical efficacy and safety | Randomized controlled trial (RCT) and cohort study |

**Table 1 The comparison between ID and SD of EC-MPS**

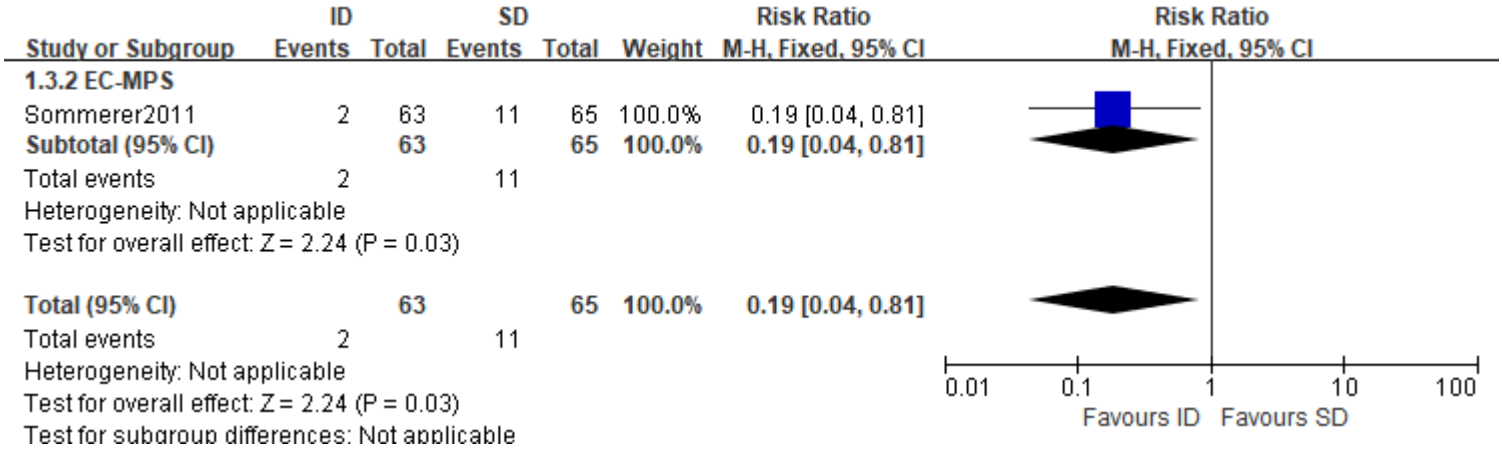
| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **Treatment failure**<br>1 RCT[1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 19/63 | 24/65 | 0.82 [0.50, 1.34] | Moderate<br>⊕⊕⊕○ |
| **BPAR**<br>1 RCT[1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 2/63 | 11/65 | 0.19 [0.04, 0.81] | Moderate<br>⊕⊕⊕○ |
| **BPAR**<br>1 cohort study[2] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 2/82 | 13/127 | 0.24 [0.06, 1.03] | Very low<br>⊕○○○ |
| **Graft loss**<br>1 RCT[1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 2/63 | 3/65 | 0.69 [0.12, 3.98] | Moderate<br>⊕⊕⊕○ |
| **MPA discontinuation**<br>1 RCT[1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 15/63 | 11/65 | 1.41 [0.70, 2.82] | Moderate<br>⊕⊕⊕○ |
| **Death** | Not serious | Not applicable | Not serious | Serious | Undetected | None | 1/63 | 2/65 | 0.52 [0.05, 5.55] | Moderate |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| 1 RCT[1] | | | | | | | | | | ⊕⊕⊕○ |
| **Overall AEs**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 101/101 | 102/102 | 1.00 [0.97, 1.03] | Moderate<br>⊕⊕⊕○ |
| **Overall infection**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 65/101 | 80/102 | 0.82 [0.69, 0.98] | Moderate<br>⊕⊕⊕○ |
| **Overall infection**<br>2 cohort studies[2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 38/119 | 60/187 | 0.99 [0.71, 1.38] | Very low<br>⊕○○○ |
| **Overall hematological AEs**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 47/101 | 46/102 | 1.03 [0.77, 1.39] | Moderate<br>⊕⊕⊕○ |
| **Overall GI AEs**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 79/101 | 73/102 | 1.09 [0.93, 1.28] | Moderate<br>⊕⊕⊕○ |
| **CMV infection**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 6/101 | 12/102 | 0.51 [0.20, 1.30] | Moderate<br>⊕⊕⊕○ |
| **BK infection**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 6/101 | 1/102 | 4.40 [0.76, 25.34] | Moderate<br>⊕⊕⊕○ |
| **Urinary tract infection**<br>1 RCT[1] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 27/63 | 28/65 | 0.99 [0.67, 1.48] | Moderate<br>⊕⊕⊕○ |
| **Anemia**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 25/101 | 29/102 | 0.87 [0.55, 1.38] | Moderate<br>⊕⊕⊕○ |
| **Anemia**<br>1 cohort study[2] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 5/82 | 7/127 | 1.11 [0.36, 3.37] | Very low<br>⊕○○○ |
| **Leucopenia** | Not serious | Not serious | Not serious | Serious | Undetected | None | 21/101 | 23/102 | 0.92 [0.55, 1.56] | Moderate |

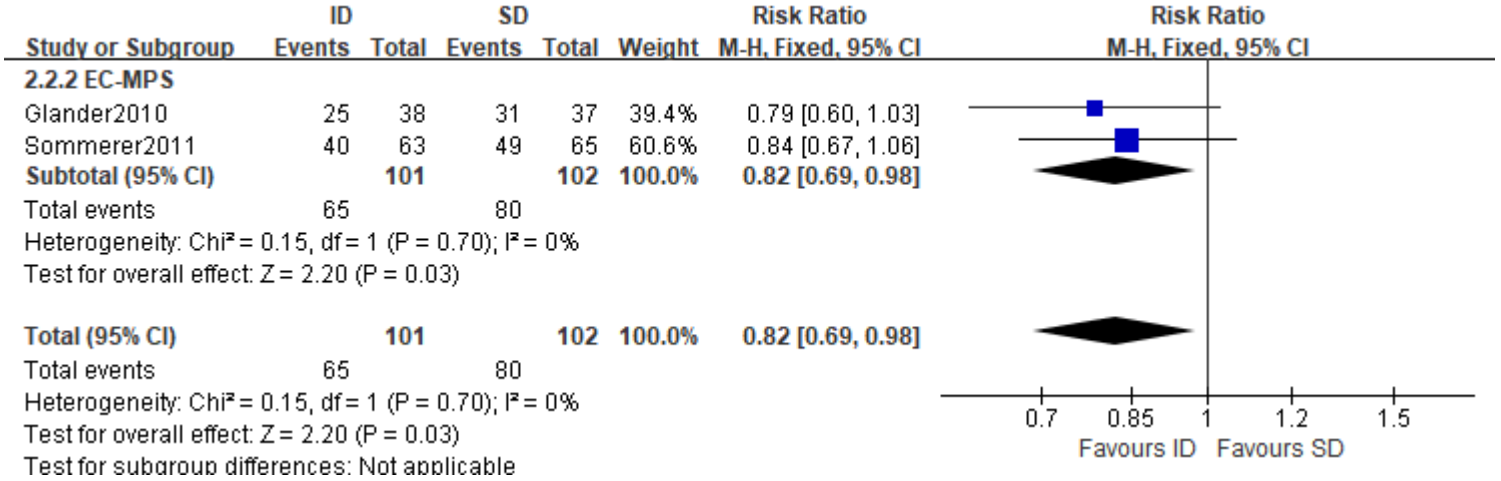
| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative Risk (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| 2 RCTs[1,3] | | | | | | | | | | ⊕⊕⊕○ |
| **Leucopenia**<br>1 cohort study[2] | Not serious | Not applicable | Not serious | Serious | Undetected | None | 6/82 | 8/127 | 1.16 [0.42, 3.23] | Very low<br>⊕○○○ |
| **Thrombocytopenia**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 7/101 | 1/102 | 5.04 [0.89, 28.58] | Moderate<br>⊕⊕⊕○ |
| **Diarrhea**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 39/101 | 37/102 | 1.06 [0.74, 1.52] | Moderate<br>⊕⊕⊕○ |
| **Diarrhea**<br>2 cohort studies[2,4] | Not serious | Not serious | Not serious | Serious | Undetected | None | 26/119 | 32/187 | 1.28 [0.81, 2.03] | Very low<br>⊕○○○ |
| **Nausea**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 35/101 | 31/102 | 1.14 [0.77, 1.70] | Moderate<br>⊕⊕⊕○ |
| **Vomiting**<br>2 RCTs[1,3] | Not serious | Not serious | Not serious | Serious | Undetected | None | 24/101 | 26/102 | 0.93 [0.58, 1.51] | Moderate<br>⊕⊕⊕○ |

BPAR, biopsy-proven acute rejection; MPA, mycophenolic acid; AE, adverse event; GI, gastrointestinal; CMV, cytomegalovirus; BK, BK polyomavirus.

## Supplemental Figure 1: BPAR for ID vs SD




## Supplemental Figure 2: Overall infection for ID vs SD



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## Recommendation 12

## Question 12*: What is the clinical benefit of dosing based on body weight (BW)?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Renal transplant recipients treated with Mycophenolic Acid (MPA) | Underweight or obese recipients | Normal weight recipients | Pharmacokinetic (PK) parameters |

**Table 1 The effect of body weight on pharmacokinetics of MPA**

| Studies (Author year) | Population | Groups | PK indicators | Quality of evidence |
|---|---|---|---|---|
| Yamada 2016[1] 1 RCT | Renal transplant (n=44) | BW<50 kg(n=11) vs BW 50-60 kg(n=20 ) vs BW ⩾ 60 kg(n=12) | MPA AUC: MMF dose: 0.080±0.035 μg•h/mL/mg vs 0.064±0.029 μg•h/mL/mg vs 0.051±0.014 μg•h/mL/mg(*P*<0.05) | Low ⊕⊕○○ |
| Kaplan 2010[2] 1 cohort study | Renal transplant (n=219) | BW⩽5 0kg (n=12) vs BW 60-80 kg (n=136) vs BW⩾100 kg (n=71) | ① AUC: 85.3±36.6 mg•h/L vs 57.7±22.5 mg•h/L vs 46.2±18.8 mg•h/L(*P*<0.0001) ② Oral clearance:13.78±5.8 L/h vs 20.15±9.10 L/h vs 25.70±12.47 L/h(*P*<0.0001) | Moderate ⊕⊕⊕○ |

RCT, randomized controlled trial; AUC, area under the curve; MMF, mycophenolate mofetil.

## References

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## Recommendation 13

## Question 13*: Should Pharmacokinetic (PK) characteristics be considered in renal transplant recipients with specific physiological conditions?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Solid organ transplant recipients treated with MPA | Recipients with specific physiological conditions: pediatric, elderly, pregnancy, breastfeeding, kidney impairment, liver impairment, hypoalbuminemia, neutropenia, etc. | Adult | PK parameters: area under the curve (AUC), Cmax, Tmax, C0, etc. |

**Table 1 The pharmacokinetic characteristics of elderly renal transplant recipients and renal transplant recipients with renal dysfunction**

| Physiological conditions | Studies (Author year) | Design | Population (intervention vs control) | MPA dosage form | Conclusion | Quality of evidence |
|---|---|---|---|---|---|---|
| Elderly vs Younger control group | Tang 2017[1] | Cohort study | Elderly, 60.1-76.2 yr (n=26) vs Adult, 19.2-58.4 yr (n=51) | MMF | Age did not significantly affect the PK or PD of MPA, including MPA AUC. Younger and elderly patients have a comparable MPA exposure when treated with similar MMF doses. | Moderate |
| | Romano 2019[2] | RCT | Elderly, 65 ± 3 yr (n=44) vs Adult, 35 ± 6 yr (n=31) | EC-MPS | The pharmacokinetic parameters of MPA adjusted for dose and weight in elderly recipients who received EC-MPS did not differ from those obtained for a control group of younger adults. | Low |
| Renal dysfunction vs Normal renal function | Van 2011[3] | RCT | DGF n=187 vs Non-DGF n=643 | MMF | Patients with DGF have significantly lower dose-corrected MPA AUC in day 3, day 10 and week 4 after renal transplantation. | Low |
| | Mohammad 2008[4] | Cohort study | Severe renal impairment | MMF | MPA $AUC_{0-12h}$、MPA $AUC_{0-6h}$、$C_{max1}$，$C_{max2}$ was significantly higher in group | Moderate |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (GFR＜30ml/min, n=13) vs Normal renal function (GFR＞70ml/min, n=13) | | impaired while MPA plasma clearance was higher in group control (P<0.05). | |
| | González 2005[5] | Cohort study | Severe renal insufficiency (CrCl＜30ml/min, n=10) vs Preserved renal function (CrCl＞90 ml/min, n=10) | MMF | MPAG $C_0$, f-MPA $AUC_{0-12h}$ were significantly higher in the renal insufficiency group, the mean $AUC_{0-12h}$ for f-MPA doubled than then control group. f-MPA $C_{min}$ was significantly higher (by fourfold) in the renal insufficiency group. | Moderate |
| | González 2007[6] | Cohort study | Advanced renal insufficiency (CrCl 27±5 ml/min, n=10) vs Preserved renal function (CrCl 105±7 ml/min, n=10) | MMF | There was no difference in MMF dose or MPA $AUC_{0-12h}$ between groups. Mean predose levels of AcMPAG-$C_0$ and AcMPAG $AUC_{0-12h}$ were much higher in recipients with advanced renal insufficiency. | Moderate |
| | Busaya 2019[7] | Cohort study | CrCl< 25 ml/min, n=17 vs CrCl≥25 ml/min, n=25 | MMF | Reduced renal function is found to significantly decrease the MPA AUC early after transplantation (*P*=0.017). The MPA clearance is 34% higher in patients with CrCl＜25 mL/min when compared with those who had better renal function. | Moderate |
| | Jiao 2018[8] | Cohort study | DGF n=23 vs Non-DGF n=38 | EC-MPS | Though MPA $AUC_{0-12\ h}$, $C_0$, $C_{min}$, $C_{max}$, $T_{max}$, and EC-MPS doses showed no significant differences, the proportion of patients with MPA $AUC_{0-12\ h}$ below 30 mg•h/L at one week after transplantation in the DGF group was significantly lower than that in the no-DGF group. Early low exposure to EC-MPS was related to acute graft rejection in the recipients at a high risk of DGF. | Moderate |

Yr, years old; PK, pharmacokinetics; PD, pharmacodynamics; RCT, random clinical trials; GFR, glomerular filtration rate; Crcl, creatinine clearance; f-MPA, free fraction of MPA; EC-MPS, enteric-coated mycophenolate sodium; AcMPAG, acyl-glucuronide MPA.

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## Recommendation 14

## Question 14*: Should (MPA) dosage be individualized during treatment?

| Population | Intervention/ Comparison | Outcomes |
|---|---|---|
| Solid organ transplant recipients treated with MPA | Different dose adjustment methods | Clinical efficacy, safety, pharmacokinetic/pharmacodynamic (PK/PD) parameters |

### References

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## Recommendation 15

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

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Solid organ transplant recipients treated with MPA | Wild-type genotype | Mutant genotype | Clinical efficacy, safety, pharmacokinetic/pharmacodynamic (PK/PD) parameters |

**Table 1 Effect of different genotypes on clinical outcomes in renal transplant recipients**

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **1. IMPDH1** | | | | | | | | | | |
| **AR**<br>**(n=3) *IVS7 +125G>A***<br>**AA/GA vs GG** | Not serious | Serious | NR | Not serious | NR | None | 264 | 132 | 0.599 [0.290, 1.239] | Very low<br>⊕○○○ |
| **Leukopenia**<br>**(n=2) *IVS7 +125G>A***<br>**AA/GA vs GG** | Not serious | Serious | NR | Serious | NR | None | 161 | 88 | 1.132 [0.443, 2.895] | Very low<br>⊕○○○ |
| **AR**<br>**(n=2) *IVS8 -106G>A***<br>**AA/GA vs GG** | Not serious | Serious | NR | Serious | NR | None | 162 | 89 | 0.826 [0.251, 2.712] | Very low<br>⊕○○○ |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **leukopenia**<br>**(n=2) *IVS8 -106G>A***<br>**AA/GA vs GG** | Not serious | Serious | NR | Serious | NR | None | 151 | 98 | 1.188 [0.517, 2.730] | Very low<br>⊕○○○ |
| **Leukopenia**<br>**(n=2) *IVS5 -227C>T***<br>**TT/CT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 73 | 176 | 0.876 [0.464, 1.653] | Very low<br>⊕○○○ |
| **Leukopenia**<br>**(n=2) *1572C>T***<br>**TT/CT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 108 | 141 | 1.246 [0.783, 1.981] | Very low<br>⊕○○○ |
| **2. IMPDH2 (*3757T>C*)** | | | | | | | | | | |
| **AR**<br>**(n=5) CC/CT vs TT** | Not serious | Serious | NR | Not serious | NR | None | 110 | 664 | 0.914 [0.398, 2.098] | Very low<br>⊕○○○ |
| **GI AEs**<br>**(n=2) CC/CT vs TT** | Not serious | Not serious | NR | Serious | NR | None | 22 | 147 | 0.968 [0.480, 1.950] | Very low<br>⊕○○○ |
| **Leukopenia**<br>**(n=3) CC/CT vs TT** | Not serious | Not serious | NR | Not serious | NR | None | 40 | 311 | 0.682 [0.378, 1.231] | Low<br>⊕⊕○○ |
| **3. SLCO1B1 (*521C>T,* N=3; *388G>A,* n=2)** | | | | | | | | | | |
| **GI AEs**<br>**CC vs TT** | Not serious | Not serious | NR | Serious | NR | None | 15 | 250 | 0.931 [0.314, 2.761] | Very low<br>⊕○○○ |
| **GI AEs** | Not serious | Not serious | NR | Not serious | NR | None | 127 | 250 | 1.482 [0.859, 2.558] | Low |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **TC vs TT** | | | | | | | | | | ⊕⊕○○ |
| **GI AEs**<br>**GG vs AA** | Not serious | Not serious | NR | Serious | NR | None | 32 | 12 | 1.503 [0.371, 6.097] | Very low<br>⊕○○○ |
| **GI AEs**<br>**AG vs AA** | Not serious | Not serious | NR | Serious | NR | None | 67 | 12 | 1.701 [0.454, 6.376] | Very low<br>⊕○○○ |
| **4. SLCO1B3 (*334T>G*, n=3)** | | | | | | | | | | |
| **GI AEs**<br>**GG vs TT** | Not serious | Serious | NR | Not serious | NR | None | 84 | 243 | 1.233 [0.530, 2.866] | Very low<br>⊕○○○ |
| **GI AEs**<br>**TG vs TT** | Not serious | Not serious | NR | Not serious | NR | None | 177 | 243 | 0.622 [0.412, 0.940] | Low<br>⊕⊕○○ |
| **5. SLCO2B1 (*1457C>T*, n=2)** | | | | | | | | | | |
| **GI AEs**<br>**TT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 15 | 80 | 0.445 [0.117, 1.686] | Very low<br>⊕○○○ |
| **GI AEs**<br>**CT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 72 | 80 | 0.972 [0.594, 1.589] | Very low<br>⊕○○○ |
| **6. ABCB1 (*3435C>T*, n=2)** | | | | | | | | | | |
| **AR**<br>**TT/CT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 186 | 70 | 1.815 [1.023, 3.219] | Very low<br>⊕○○○ |
| **GI AEs**<br>**TT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 98 | 105 | 1.269 [0.784, 2.054] | Very low<br>⊕○○○ |

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Relative effect (RR) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **GI AEs**<br>**CT vs CC** | Not serious | Not serious | NR | Not serious | NR | None | 209 | 105 | 1.042 [0.671, 1.618] | Low<br>⊕⊕○○ |
| **7. ABCC2 (-24T>C, n=4)** | | | | | | | | | | |
| **GI AEs**<br>**TT/CT vs CC** | Not serious | Not serious | NR | Not serious | NR | None | 137 | 185 | 1.233 [0.839, 1.811] | Low<br>⊕⊕○○ |
| **8. UGT1A9 (*-275T>A/-2152C>T,* n=2)** | | | | | | | | | | |
| **AR**<br>**TA/CT vs TT/CC** | Not serious | Not serious | NR | Serious | NR | None | 14 | 100 | 2.454 [0.951, 6.335] | Very low<br>⊕○○○ |
| **9. UGT2B7 (*802C>T,* n=2)** | | | | | | | | | | |
| **AR**<br>**TT/CT vs CC** | Not serious | Not serious | NR | Serious | NR | None | 77 | 59 | 0.679 [0.228, 2.024] | Very low<br>⊕○○○ |
| **10. CYP3A5 (*6986A>G,* n=2)** | | | | | | | | | | |
| **AR**<br>**GG vs AA/AG** | Not serious | Not serious | NR | Serious | NR | None | 204 | 49 | 1.498 [0.564, 3.976] | Very low<br>⊕○○○ |

IMPDH, inosine monophosphate dehydrogenase; AR, acute rejection; NR, not reported; GI AEs, gastrointestinal adverse events

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## Recommendation16

## Question 16*: Is it necessary to evaluate the effect of co-administration on the blood concentration of mycophenolic acid (MPA)?

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

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Solid organ transplant recipients treated MPA | Co-administration | Without co-administration | Clinical efficacy, safety, pharmacokinetic/pharmacodynamic (PK/PD) parameters |

**Table 1 Comparison of clinical parameters between PPIs exposure and non-exposure on MPA**

| Outcomes<br>No. of studies, design | Quality assessment | | | | | | Summary of findings | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Upgrading | Sample size | | Mean Difference (MD) | Quality of evidence |
| | | | | | | | Intervention | Comparator | | |
| **dAUC MMF**<br>2 RCTs [1-2] | Serious | Not serious | Not serious | Serious | Undetected | None | 36 | 36 | -4.69 [-17.26, 7.88] | Low<br>⊕⊕○○ |
| **dAUC EC-MPS**<br>2 RCTs [1-2] | Serious | Not serious | Not serious | Serious | Undetected | None | 38 | 38 | 4.28 [-8.30, 16.86] | Low<br>⊕⊕○○ |
| **$dC_{max}$ MMF**<br>2 RCTs [1-2] | Serious | Not serious | Not serious | Not serious | Undetected | None | 36 | 36 | -3.59 [-7.91, 0.73] | Moderate<br>⊕⊕⊕○ |
| **$dC_{max}$ EC-MPS**<br>2 RCTs [1-2] | Serious | Not serious | Not serious | Not serious | Undetected | None | 38 | 38 | 2.14 [-3.80, 8.07] | Moderate<br>⊕⊕⊕○ |

PPIs, proton pump inhibitors; MMF, mycophenolic mofetil; dAUC, dose-normalized AUC; $dC_{max}$, dose-normalized $C_{max}$

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# Part IV Conflicts of interest

| **Conflict of Interest Statement Form** |
| --- |
| Dear Guideline Members:<br>Hello! Thank you very much for your support of the Mycophenolic Acid Therapeutic Drug Monitoring Guideline project. This guideline will be developed in strict compliance with the methodological specifications of international clinical practice guidelines such as the WHO Handbook for Guideline Development. The declaration and management of conflicts of interest are important guarantees for the quality, credibility and authority of clinical practice guidelines. In order to ensure the standardization of the preparation of this guide, please fill out and sign the "Conflict of Interest Declaration Form" of this guideline at your convenience. |
| Details of conflict of interest statement |
| Please declare in this form any financial, academic, or other interests that may have influenced the development of this guideline (and your advisory opinions/suggestions in the development of future related policies). |
| 1. In the past year: I (have) held shares/stocks of companies that have an interest in this guide [Single choice question] * |
| ○Yes |
| ○No |
| 2. In the past year: I (have) served as a consultant for a company that has an interest in this guide and received corresponding remuneration [Single-choice question] * |
| ○Yes |
| ○No |
| 3. In the past year: I (have) received research funding from companies that have an interest in this guideline [Single-choice question] * |
| ○Yes |
| ○No |
| 4. In the past year: I (have) accepted other expenses (travel expenses, etc., > 10,000 yuan) from companies that have an interest in this guideline [Single-choice question] * |
| ○Yes |
| ○No |

| |
|---|
| 5. In the past year: I have academic or other interests that may affect the objectivity of this guideline [Single-choice question] * |
| ○Yes |
| ○No |
| 6. If your answer to any of the above questions is "yes", please provide a brief explanation in the box below (if not, please fill in "none"). [Fill in the blank] * |
| _____ |
| 7. If you have other content or matters that need to be declared, please fill in the box below (if not, please fill in "none"). [Fill in the blank] * |
| _____ |
| I declare: I promise that the content I declare is true and complete, and agree to be disclosed in an appropriate form in the final text of the guideline. If there are any changes to what I have declared above before the guideline is finalized, I will promptly contact the guideline secretarial team and fill in the updated conflict of interest declaration form.<br><br>Your autograph: |

# Part V Recommendation consensus

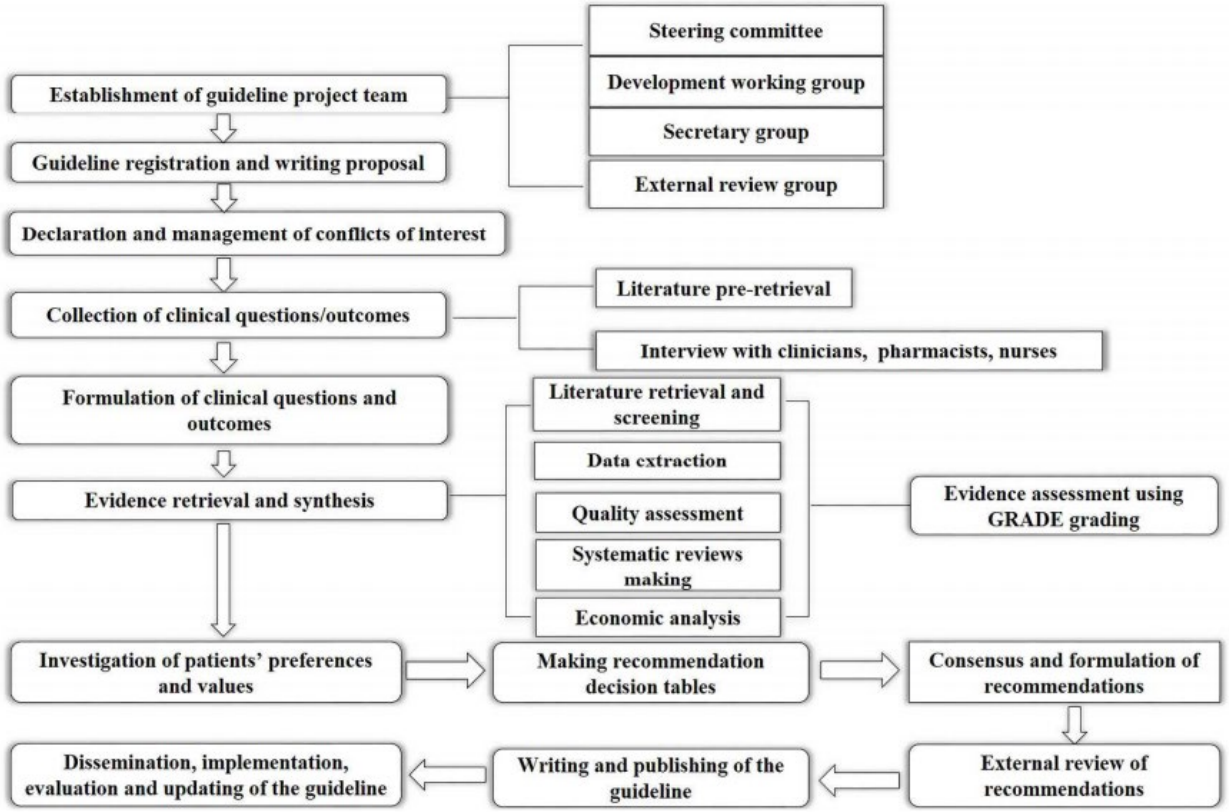


**Figure 1 Flowchart of guideline development process**

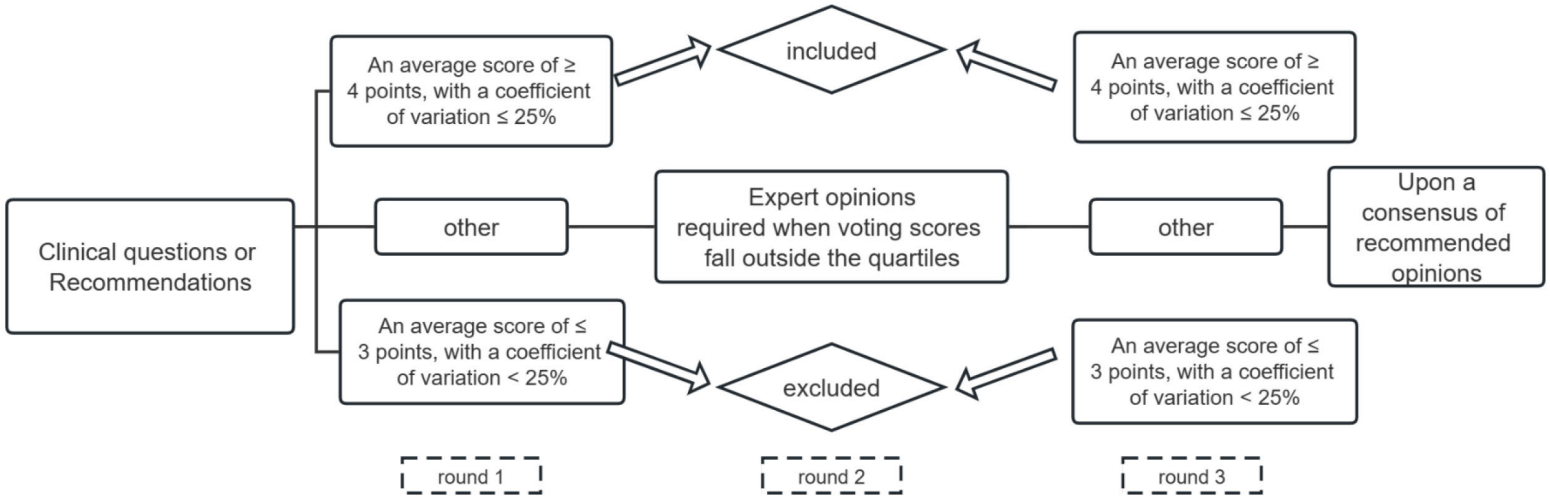


**Figure 2 Process of Delphi method**

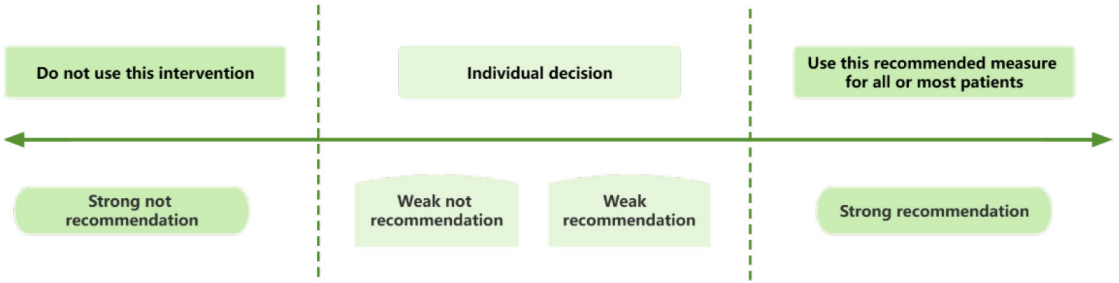


**Figure 3 Recommendation strength and direction based on the GRADE evaluation system**