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# Efficacy and safety of conventional antiviral agents in preventive strategies for cytomegalovirus infection after kidney transplantation: a systematic review and network meta-analysis

Narisa Ruenroengbun[1,2], Pawin Numthavaj[1], Tunlanut Sapankaew[1], Kamolpat Chaiyakittisopon[1,3], Atiporn Ingsathit[1], Gareth J. Mckay[4], John Attia[5] & Ammarin Thakkinstian[1]

1 Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
2 Department of Pharmaceutics, Clinical Pharmacy, Slipakorn University, Nakorn Prathom, Thailand
3 Department of Community Pharmacy and Administrations, Faculty of Pharmacy, Slipakorn University, Nakorn Prathom, Thailand
4 School of Medicine, Dentistry and Biomedical Sciences, Center for Public Health, Queen's University Belfast, Belfast, UK
5 School of Medicine and Public Health, Centre for Clinical Epidemiology and Biostatistics, Hunter Medical Research Institute, University of Newcastle, New Lambton, NSW, Australia

**Correspondence**
Pawin Numthavaj MD, PhD, Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Rachatevi, Bangkok 10400, Thailand.
Tel.: +6622011762;
fax: +6622011284;
e-mail: pawin.num@mahidol.ac.th

## SUMMARY

Cytomegalovirus (CMV) infection is common in kidney transplantation (KT). Antiviral-agents are used as universal prophylaxis. Our purpose aimed to compare and rank efficacy and safety. MEDLINE, Embase, SCOPUS, and CENTRAL were used from inception to September 2020 regardless language restriction. We included randomized clinical trials (RCTs) comparing the CMV infection/disease prophylaxis among antiviral-agents in adult KT recipients. Of 24 eligible RCTs, prophylactic valganciclovir (VGC) could significantly lower the overall CMV infection and disease risks than placebo with pooled risk differences (RDs) [95% confidence interval (CI)] of −0.36 (−0.54, −0.18) and −0.28 (−0.48, −0.08), respectively. Valacyclovir (VAC) and ganciclovir (GC) significantly decreased risks with the corresponding RDs of −0.25 (−0.32, −0.19) and −0.30 (−0.37, −0.22) for CMV infection and −0.26 (−0.40, −0.12) and −0.22 (−0.31, −0.12) for CMV disease. For subgroup analysis by seropositive-donor and seronegative-recipient (D+/R−), VGC and GC significantly lowered the risk of CMV infection/disease with RDs of −0.42 (−0.84, −0.01) and −0.35 (−0.60, −0.12). For pre-emptive strategies, GC lowered the incidence of CMV disease significantly with pooled RDs of −0.33 (−0.47, −0.19). VGC may be the best in prophylaxis of CMV infection/disease follow by GC. VAC might be an alternative where VGC and GC are not available.

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**Key words**
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## Introduction

Kidney transplants (KT) accounted for 69,400 out of 100,800 (62.5%) solid organ transplants globally [1]. Unfortunately, opportunistic infections after KT do occur, in which Cytomegalovirus (CMV) is the most common, leading to allograft dysfunction, graft rejection, and even death [2–4]. Recipients are at high risk




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of CMV infection in the 3–6 month period after KT if they were CMV seronegative (R−) but received organs from CMV seropositive donors (D+); called as D+/R−, or received induction therapy [e.g., lymphocyte-depleting agent or anti-thymocyte globulin (ATG)] [5–7]. Prophylactic and pre-emptive strategies have been developed to decrease the risk of CMV infection after transplantations [8]. The afore mentioned strategies in the former administering antiviral agents will be implemented immediately after transplant for 3–6 months, whereas the latter consists of administering antiviral agents when CMV is detected [9,10].

Antiviral agents including valganciclovir (VGC), valacyclovir (VAC), ganciclovir (GC), and acyclovir (AC) have been studied in prophylactic regimens or pre-emptive regimens [11–14]. Although the third International Consensus Guidelines on the Management of CMV in Solid-organ Transplantation [15], the Kidney Disease Improving Global Outcomes and clinical practice guidelines for KT [16] recommend that VGC and GC are considered as the first and second-line drugs [17,18], in lower-middle-income countries, this has not been widely adopted given that VGC is high cost, has multiple adverse effects (e.g., anemia, neutropenia, leukopenia, thrombocytopenia, and hallucination) and limited healthcare infrastructures. Likewise, GC is available in only intravenous form [19–21]. For these reasons, VAC and AC, have been studied to use as universal prophylaxis, as they were still prescribed in developing countries for prophylaxis of CMV infection/disease [22,23] with less bone marrow suppression than GC [24]. Although previous systematic reviews (SR) and meta-analyses (MA) have assessed the efficacy of some antiviral agents, and pooled all solid organ transplants without focusing specifically on KT [25–28]. Additionally, none of the previous SR-MAs summarized the efficacy of anti-CMV prophylaxis in subgroups of prophylaxis periods [i.e., early onset CMV infection (≤6 months), and late-phase infection (>6 months)], and high-risk patients (D+/R−). Furthermore, none had performed treatment ranking for the most effective and safest antiviral agents. Therefore, we performed this SR and network meta-analysis (NMA) to rank the efficacy and safety of anti-CMV prophylaxis agents with a focus on KT recipients. Additionally, none of the previous SR-MAs performs risk-benefit analysis between the risk of adverse effect and benefit from lowering the incidence of CMV infection because of prolonged use of antiviral agents in the prophylaxis. Therefore, this study aimed to evaluate the risk-benefit of CMV prophylaxis [29,30].

## Methodology

### Search strategies and study selection

We searched MEDLINE via PubMed, Embase, SCOPUS, and the Cochrane Central Registry of Controlled Trials (CENTRAL) without language restriction up to September 2020. Search terms were constructed based on patients ("kidney transplantation (KT)", "CMV infection") and interventions ("prophylaxis," "pre-emptive," "VGC," "VAC," "GC," and "acyclovir"), see Table S1. Randomized clinical trials (RCTs) and quasi-RCT were eligible if they studied in adult KT recipients, compared any pair of following interventions (i.e., VGC, VAC, GC, AC, and placebo/control (PC) for CMV prophylaxis/pre-emptive purpose, and had at least one outcome (i.e., CMV infection or CMV disease). Studies were excluded if they used other antiviral agents (e.g., cidofovir, brincidofovir, and foscarnet), combined antiviral agents with intravenous immunoglobulin therapy, or compared the same drug with different regimens, see Table S2. This study has been registered with PROSPERO (CRD42019145845) and was exempted from Ramathibodi hospital ethics committee board.

### Interventions and outcomes

Antiviral agents of interest were VGC (900 mg once daily), high dose VAC (2000 mg four times a day), oral GC (1000 mg three times daily), or IV GC (2.5–5.0 mg/kg/dose once or two times daily), AC (200–800 mg four times daily), and combinations thereof, see Table 1. The primary outcomes were CMV infection, which could occur in the early (i.e., ≤6 months) or late-phase (>6 months to 4 years) or CMV disease after KT, see Table S3 for definition [31–33]. The secondary outcome was a composite of major adverse effects including neutropenia, thrombocytopenia, leucopenia, anemia, and hallucination.

### Data extraction and Risk of bias assessment

Two of three reviewers (i.e., NR, TS, and KC) independently extracted data on each study. Any disagreement was discussed and resolved by a third party (PN). Data extracted included prevention strategies, type of transplants, interventions (dose, duration, and route of administration), follow-up time, and outcomes. Digitizer software was used to extract information from Kaplan-Meier survival plots [34].

**Table 1.** Characteristics of included studies.

| Authors year | Graft | Outcomes | Total | Intervention | Comparator | Follow up time (months) | Strategy | D+/ R+ | D−/ R+ | D+/ R− | D−/ R− | Deceases donor | % Of Induction | Country |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prophylaxis | | | | | | | | | | | | | | |
| 1. Pettersson 1985 [46] | KT | CMV infection CMV disease | 35 | Acyclovir 200 mg Q.I.D | Control | 1 m | Prophylaxis | NA | | | | NA | NA | USA |
| 2. Balfour 1989 [47] | KT | CMV infection CMV disease | 104 | Acyclovir 200–800 mg Q.I.D | Control | 3–12 m | Prophylaxis | 31 | 43 | 30 | 0 | 104 | 8.65 | USA |
| 3. Rondeau 1993 [43] | KT | CMV infection CMV disease | 32 | IV Ganciclovir 5 MKD B.I.D | Control | 3–12 m | Prophylaxis | 0 | 0 | 32 | 0 | 32 | 18.8 | France |
| 4. Rostaing 1994 [49] | KT | CMV infection CMV disease | 37 | Acyclovir 800 mg Q.I.D | Control | 3–12 m | Prophylaxis | 17 | 20 | 0 | 0 | 37 | 100 | France |
| 5. Conti 1994 [40] | KT | CMV infection CMV disease | 47 | IV Ganciclovir 2.5 MKD | Control | 12 m | Prophylaxis | 0 | 47 | 0 | 0 | 37 | 100 | USA |
| 6. Conti 1995 [41] | KT | CMV infection CMV disease | 40 | IV Ganciclovir 2.5 MKD | Control | 12 m | Prophylaxis | 40 | | 0 | 0 | 37 | 95.0 | USA |
| 7. Jiang 1995 [50] | KT | CMV infection | 66 | Acyclovir 200 mg T.I.D-Q.I.D | Control | 3 m | Prophylaxis | NA | | | | NA | NA | China |
| 8. Leray 1995 [45] | KT | CMV infection CMV disease | 23 | IV Ganciclovir 5 MKD B.I.D | Control | 6 m | Prophylaxis | 0 | 0 | 23 | 0 | NA | 100 | France |
| 9. Kletzmayr 1996 [48] | KT | CMV infection CMV disease | 32 | Acyclovir 200–800 mg Q.I.D | Control | 3–12 m | Prophylaxis | 0 | 0 | 32 | 0 | NA | NA | Austria |
| 10. Ahsan 1997 [44] | KT | CMV infection CMV disease | 43 | Ganciclovir 750 mg B.I.D | Control | 6 m | Prophylaxis | 13 | 10 | 8 | 12 | 33 | 11.6 | USA |
| 11. Brennan 1997 [42] | KT | CMV infection CMV disease | 42 | Ganciclovir 1000 mg T.I.D | Control | 3–6 m | Prophylaxis | 24 | 13 | 5 | 0 | 25 | 7.14 | USA |
| 12. Conti 1997 [39] | KT | CMV disease | 244 | IV Ganciclovir 2.5 MKD B.I.D | Control | 12 m | Prophylaxis | 244 | | 0 | 0 | 181 | NA | USA |
| 13. Flechner 1998 [51] | KT | CMV infection CMV disease | 101 | Ganciclovir 1000 mg T.I.D | Acyclovir 800 mg Q.I.D | 3–6 m | Prophylaxis | 29 | 23 | 27 | 0 | 83 | 100 | USA |
| 14. Lowance 1999 [17] | KT | CMV infection CMV disease | 616 | Valacyclovir 2000 mg Q.I.D | Control | 3–6 m | Prophylaxis | 408 | | 208 | | 616 | 16.6 | USA and Europe |
| 15. Rubin 2000 [52] | KT | CMV infection CMV disease | 89 | Ganciclovir 1000 mg T.I.D | Acyclovir 400 mg T.I.D | 6 m | Prophylaxis | 0 | 0 | 89 | 0 | 45 | NA | USA |
| 16. Paya 2004 [56] | KT, LT | CMV disease | 120 | Valganciclovir 900 mg O.D. | Ganciclovir 1000 mg T.I.D | 6 m | Prophylaxis | 0 | 0 | 120 | 0 | NA | NA | USA |

**Table 1.** Continued.

| Authors year | Graft | Outcomes | Total | Intervention | Comparator | Follow up time (months) | Strategy | D+/R+ | D−/R+ | D+/R− | D−/R− | Deceases donor | % Of Induction | Country |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17. Pavlopoulou 2005 [54] | KT | CMV infection CMV disease | 83 | Valacyclovir 2000 mg Q.I.D | Ganciclovir 1000 mg T.I.D | 3–6 m | Prophylaxis | 12 | 47 | 16 | 8 | 32 | 85.5 | Greece |
| 18. Reischig 2005 [53] | KT | CMV infection CMV disease | 83 | Valacyclovir 2000 mg Q.I.D | Ganciclovir 1000 mg T.I.D | 12 m | Prophylaxis | 60 | 13 | 10 | 0 | 79 | 12.7 | Czech |
| 19. Reischig 2018 [55] | KT | CMV infection CMV disease | 119 | Valganciclovir 900 mg O.D. | Valacyclovir 2000 mg Q.I.D | 6 m–3 y | Prophylaxis | 93 | 15 | 11 | 0 | 111 | 50.4 | Czech |
| Pre-emptive studies | | | | | | | | | | | | | | |
| 1. Hibberd 1995 [59] | KT | CMV disease | 112 | IV Ganciclovir 2.5 MKD O.D. | Control | 6 m | Pre-emptive | 46 | 66 | 0 | 0 | 93 | 66.4 | USA |
| 2. Brennan 1997 [57] | KT | CMV disease | 36 | IV Ganciclovir 5 MKD B.I.D | Control | 3–6 m | Pre-emptive | 36 | | 0 | 0 | NA | NA | USA |
| 3. Yang 1998 [58] | KT | CMV disease | 31 | IV Ganciclovir 5 MKD B.I.D | Control | 3–6 m | Pre-emptive | 31 | 0 | 0 | 0 | NA | 58.1 | South Korea |
| 4. Koetz 2001 [60] | KT, LT | CMV disease | 10 | IV Ganciclovir 5 MKD | Control | 3–12 m | Pre-emptive | 5 | 3 | 2 | 0 | NA | NA | Germany |
| 5. Sagedal 2003 [61] | KT | CMV disease | 80 | Ganciclovir 1000 mg T.I.D | Control | 12 m | Pre-emptive | 48 | 24 | 8 | 0 | 55 | 8.75 | Norway |

B.I.D, twice a day; CMV, cytomegalovirus; CMV serologies: D+/R+, CMV seropositive donor/CMV seropositive recipients; D−/R−, CMV seronegative donor/CMV seronegative recipients; D−/R+, CMV seronegative donor/CMV seropositive recipients; D+/R−, CMV seropositive donor/CMV seronegative recipients; KT, kidney transplantation; LT, liver transplantation; m, month; mg, milligram; MKD, milligram per kilogram per dose; N, number of total patients in study; NA, data not available; O.D., once daily; Q.I.D, four times a day; T.I.D, three times a day; y, year.

The Revised Cochrane Risk-of-Bias 2 (RoB) [35] tool was implemented for quality assessment of the studies, considering five domains, i.e., randomization, deviations from the intended interventions, missing outcome data, outcome measurements, and selection of the reported results. Individual domains were graded as low, some concern, or high risk. The overall RoB was judged "low" if all domains were graded low risk, "high" if at least one of the five domains were graded high risk, and "some concern" with any other combinations.

### Statistical analysis

#### *Direct meta-analysis*

Risk differences (RD) of CMV infection/disease and 95% confidence intervals (CI) were calculated, and then they were pooled across studies using a random-effect model if heterogeneity was present (Cochrane $Q$ test $P$-value $< 0.1$ or $I^2 > 25\%$), or a fixed-effect model if heterogeneity was absent. Publication bias was assessed using funnel plots and Egger's test. If any of them showed asymmetry [36,37], a contour-enhanced funnel plot was used to further explore the cause of asymmetry [38].

#### *NMA*

Antiviral regimens of VGC, VAC, GC, AC, and PC were coded as 4, 3, 2, 1, and 0, respectively. A two-stage NMA with a consistency model was applied from the estimation of relative treatment effects (i.e., RD), and their variance-covariance for each study. A multivariate random-effect meta-analysis was applied to pool RDs across studies. The surface under the cumulative ranking curve (SUCRA) was used to rank the regimens in order of efficacy and safety. Publication bias was assessed by using a comparison-adjusted funnel plot. A cluster plot was constructed to simultaneously assess the benefit of anti-CMV prophylaxis, and the risk of major adverse effects based on SUCRA values.

#### *Risk benefit analysis*

A Monte Carlo method with 1000-simulations was compiled to simultaneously model the risk of adverse drug reactions from the first three-rank antiviral agent prophylaxis compared to the benefits of lowering CMV early onset (≤6 m) of CMV infections. A risk-benefit plane, and acceptable clinical thresholds (varied from 0.2 to 0.3), were then plotted. A sensitivity analysis was performed to pool RDs again following preventive regimens; prophylaxis, or pre-emptive. All statistical analyses were performed using STATA version 16, and risk-benefit analyses were performed using Microsoft Excel® 2013.

## Results

A total of 3726 publications were identified with 23 RCTs and 1 quasi-RCT [39] were eligible, see Fig. 1. The studies' characteristics are as followed: 19 and 5 studies used prophylaxis and pre-emptive strategies, around 54.0%, 15.0%, 30.0%, and 1.0% were D+/R+, D−/R+, D+/R−, and D−/R−, respectively. Approximate 67% of recipients received kidney organs from a deceased donor. There were 13, 6, and 5 studies reporting outcomes at ≤6 months, >6 months to 4 years, and both, respectively, see Table 1. The summary of interesting events used in the NMA is described in Table S4.

### Risk of bias

Results of RoB assessments are described in Tables S5 and S6. There was low RoB for protocol deviations, missing data, and outcome measurements in about 79.3%, 93.1%, and 72.4%, respectively. Around 26.3% of studies were rated high RoB in randomization because of lack of concealment, while 47.4% were high RoB selection of the reported results. All studies except two were rated to have at least some concern of bias.

### CMV infections among prophylaxis strategies

#### *DMA*

There was sufficient data for two direct meta-analysis (DMAs) in CMV infections, i.e., GC vs PC ($N = 6$) [40–45] and AC versus PC ($N = 5$) [46–50], see Fig. S1. Only GC was significantly lower in CMV infection than PC with a pooled RD (95% CI) of −0.27 (−0.37, −0.17), whereas AC was not significantly lower with pooled RD of −0.08 (−0.22, 0.07).

#### *NMA*

Seventeen RCTs reported overall CMV infection with rates ranging from 18.6% to 56.9%. Antiviral regimens were mapped including AC versus PC ($N = 5$) [46–50], GC versus PC ($N = 6$) [40–45], AC versus GC ($N = 2$) [51,52], VAC versus GC ($N = 2$) [53,54], VAC versus PC ($N = 1$) [17], and VAG versus VGC ($N = 1$) [55], see Fig. S2. All antiviral agents, except AC, showed significantly lower risks of CMV infection than PC with

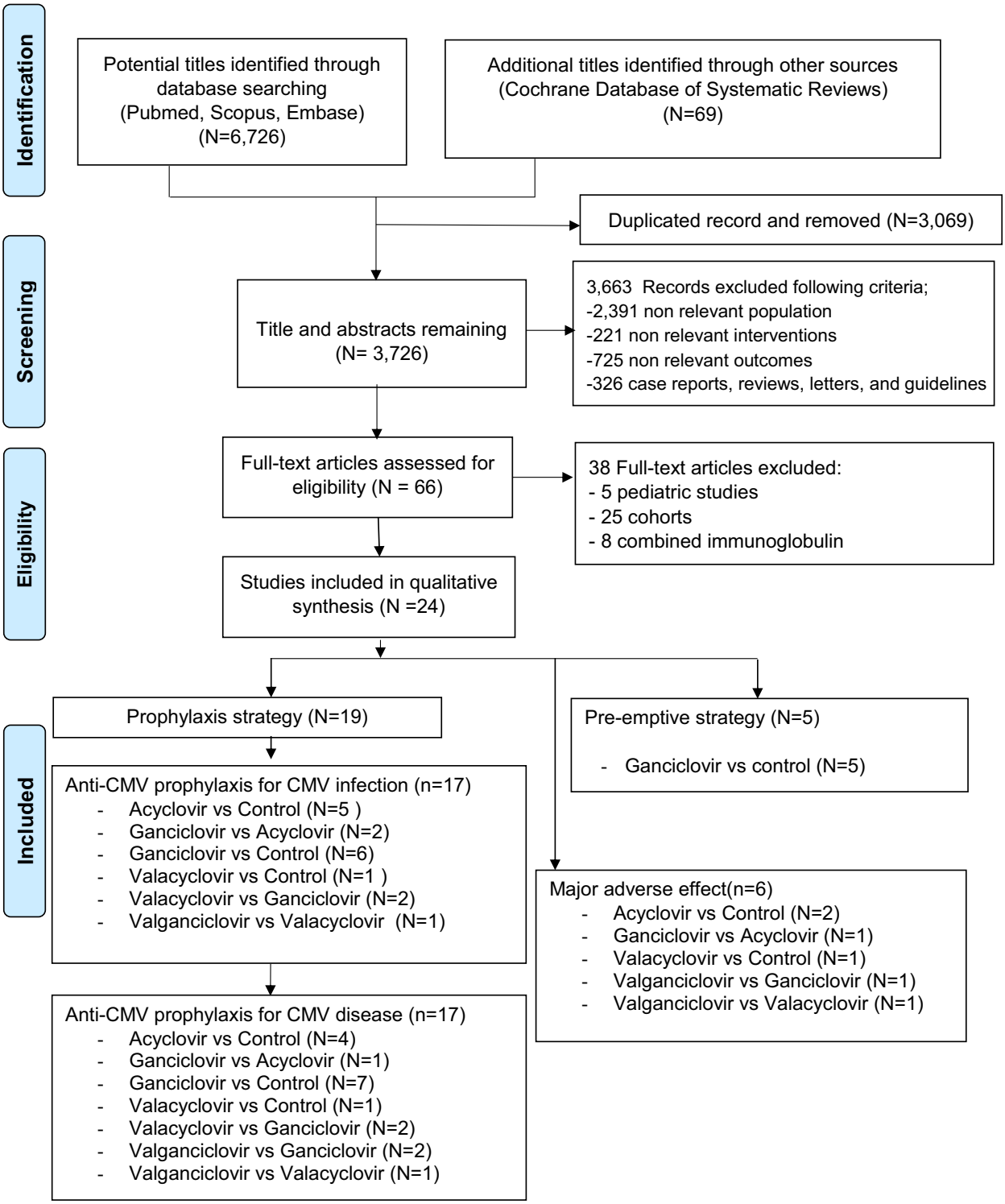


**Figure 1** PRISMA flow diagram of screening studies.

pooled RDs (95% CI) of −0.36 (−0.54, −0.18), −0.25 (−0.32, −0.19), and −0.30 (−0.37, −0.22) for VGC, VAC, and GC; NNTs were 3, 4, and 4, respectively, see Table 2. These estimate all approximate 25–35% lower risk of overall CMV infection with these drugs than PC. Furthermore, VGC, VAC, and GC showed RDs of −0.31 (−0.50, −0.11), −0.20 (−0.30, −0.10), and −0.24 (−0.33, −0.16), respectively compared to AC, approximating to 20–30% lower risks of CMV infection, see Table S7.

**Table 2.** Estimation of risk difference and NNT/N NH of any antiviral agents in CMV prophylaxis versus control: a network meta-analysis.

| | Effect sizes (95% CI) | AC | GC | VAC | VGC |
|---|---|---|---|---|---|
| CMV infection | | | | | |
| Overall CMV infection | RD | −0.052 (−0.133, 0.029) | −0.297 (−0.369, −0.224) | −0.252 (−0.316, −0.186) | −0.358 (−0.540, −0.175) |
| | NNT (95% CI) | 12 (8 NNT, 34 NNH) | 4 (3, 5) | 4 (3, 5) | 3 (2, 6) |
| Early onset (≤6 months) | RD | −0.212 (−0.400, 0.022) | −0.422 (−0.604, −0.240) | −0.342 (−0.604, −0.081) | −0.566 (−1.059, −0.072) |
| | NNT (95% CI) | 5 (3 NNT, 45 NNH) | 2 (2, 4) | 3 (2, 12) | 2 (1, 14) |
| Late phase (>6 months–4 year) | RD | 0.051 (−0.117, 0.220) | −0.315 (−0.453, −0.176) | −0.266 (−0.455, −0.076) | −0.322 (−0.579, −0.065) |
| | NNT (95% CI) | 20 (9 NNT, 5 NNH) | 3 (2, 6) | 4 (2, 13) | 3 (2, 16) |
| CMV disease | | | | | |
| CMV disease | RD | −0.075 (−0.199, 0.048) | −0.216 (−0.313, −0.118) | −0.261 (−0.399, −0.124) | −0.277 (−0.476, −0.079) |
| | NNT (95% CI) | 13 (5 NNT, 20 NNH) | 5 (3, 8) | 4 (3, 8) | 4 (2, 13) |
| Subgroup analysis (D+/R−) | | | | | |
| CMV infection/disease | RD | −0.132 (−0.436, 0.172) | −0.354 (−0.593, −0.115) | −0.268 (−0.621, 0.086) | −0.424 (−0.841, −0.010) |
| | NNT (95% CI) | 8 (2 NNT, 6 NNH) | 3 (2, 9) | 4 (2 NNT, 11 NNH) | 2 (1, 100) |
| Major ADR | | | | | |
| Major ADR | RD | −0.045 (−0.115 to 0.025) | −0.014 (−0.152, 0.124) | 0.010 (−0.050, 0.051) | 0.131 (−0.037 to 0.299) |
| | NNH (95% CI) | 22 NNT (9 NNT, 40 NNH) | NNT 71 (7 NNT, 8 NNH) | 10 NNH (20 NNT, 20 NNH) | 8 NNH (27 NNT, 3 NNH) |

AC, acyclovir; CMV, cytomegalovirus; GC, Ganciclovir; NNH, number needed to harm; NNT, number needed to treat; VAC, Valacyclovir; VGC, Valganciclovir.
Major ADR: neutropenia, thrombocytopenia, leucopenia, anemia, and hallucination.

*Subgroup analysis of NMA according to early and late-phase infection*

Fourteen and eight RCTs reported CMV infection in early and late-phase with rates ranging from 10.8% to 49.5% and 20.7% to 57.7%, respectively. For early CMV infection, antiviral regimens were mapped including AC versus PC ($N = 4$) [46,47,49,50], GC versus PC ($N = 4$) [42–45], VAC versus PC ($N = 1$) [17], AC versus GC ($N = 2$) [51,52], VAC versus GC ($N = 2$) [53,54], and VGC versus VAC ($N = 1$) [55], see Fig. S3a. All antiviral agents, except AC, showed significantly lower risks of early onset CMV infection than PC with pooled RDs (95% CI) of −0.57 (−1.06, −0.07), −0.42 (−0.60, −0.24), and −0.34 (−0.60, −0.08) for VGC, GC, and VAC, respectively, see Table 2. These estimates all approximate to 35–55% lower risk of early onset CMV infection with these drugs than PC with NNTs which were 2, 2, and 3, respectively. Furthermore, VGC, GC, and VAC showed RDs of −0.35 (−0.87, −0.16), −0.21 (−0.42, 0.00), and −0.13 (−0.43, 0.17), respectively compared to AC, approximating a 35–55% lower risk of early onset CMV infection, see Table S8.

For late CMV infection, antiviral regimens were mapped as AC versus PC ($N = 2$) [47,48], GC versus PC ($N = 3$) [40–42], VAC versus GC ($N = 2$) [53,54], and VGC versus VAC ($N = 1$) [55], see Fig. S3b. Likewise, VGC, GC, and VAC showed significantly lower risks of late CMV infection than PC with pooled RDs (95% CI) of −0.32 (−0.58, −0.07), −0.32 (−0.45, −0.18), and −0.27 (−0.46, −0.08) with NNTs which were 3, 3, and 4, respectively, see Table 2. These corresponding treatments also showed RDs of −0.37 (−0.68, −0.07), −0.37 (−0.58, −0.15), and −0.32 (−0.57, −0.06) lower than AC, approximating a 35% lower risk of late CMV infection, see Table S8. Comparison adjusted funnel plots were symmetrical, with no evidence of publication bias, see Figs S4 and S5. There was no evidence of inconsistency for overall CMV infection (Chi-square test = 0.51, $P = 0.775$), and either early onset CMV infection (Chi-square test = 5.70, $P = 0.780$) or late CMV infection (Chi-square = 0.41, $P = 0.523$) networks.

*Subgroup analysis of anti-CMV prophylaxis antiviral agents in high-risk of CMV*

Twelve RCTs included high-risk patients with D+/R− with or without receiving an induction therapy such as lymphocyte depleting agent or ATG. Antiviral regimens were mapped including AC versus PC ($N = 2$) [47,48], GC versus PC ($N = 4$) [42–45], AC versus GC ($N = 2$) [51,52], VGC versus GC ($N = 1$) [56], VAC versus PC ($N = 1$) [17], VAC versus GC ($N = 1$) [54], and VGC versus VAC ($N = 1$) [55], see Fig. S6. We found that VGC and GC showed significantly lower risks of CMV infection/disease than PC with pooled RDs (95% CI) of −0.42 (−0.84, −0.01) and −0.35 (−0.59, −0.11), respectively; while VAC was not significant with the RD of −0.27 (−0.62, 0.09), see Tables 2 and S9. There was no evidence of inconsistency in the network (Chi-square test = 1.81, $P = 0.613$).

## CMV disease among prophylaxis strategies

*DMA*

Two DMAs of CMV disease were performed, i.e., AC versus PC ($N = 4$) [46–49], and GC versus PC ($N = 7$) [39–45]. (Fig. S7) GC showed significantly lower CMV disease than PC with a pooled RD (95% CI) of −0.21 (−0.31, −0.11) while AC showed nonsignificantly lower CMV disease than PC.

*NMA*

In 16 RCTs and one quasi-RCT reported the risks of CMV disease which ranged from 4.5% to 33.1%. Antiviral regimen comparisons included AC versus PC ($N = 4$) [46–49], GC versus PC ($N = 7$) [39–45], VAC versus GC ($N = 2$) [53,54], VAC versus PC ($N = 1$) [17], GC versus AC ($N = 1$) [52], GC versus VGC ($N = 1$) [56], and VGC versus VAC ($N = 1$) [55], see Fig. S8. For overall CMC disease, all antiviral agents, except AC showed significantly lower CMV disease than PC with pooled RDs (95% CI) of −0.28 (−0.48, −0.08), −0.26 (−0.40, −0.12), and 0.22 (−0.31, −0.12) for VGC, VAC, and GC; NNTs were 4, 4, and 5, respectively, see Table 2.

Comparison adjusted funnel plots were symmetrical, suggesting no evidence of publication bias, see Fig. S9. Inconsistency assumption was not violated for the CMV disease network (Chi-square test = 9.18, $P = 0.103$).

## CMV disease among pre-emptive strategies

Five RCTs resulted in only one DMA in preventing CMV disease, GC versus PC ($N = 5$) [57–61], see Fig. S10. In this analysis, GC had a significantly lower risk in CMV disease than PC with a pooled RD (95% CI) of −0.33 (−0.47, −0.19).

## Composite major adverse effect

*NMA*

Six studies reported composite major adverse drug reactions, ranging from 11.6% to 35.0%. Antiviral

comparisons were mapped including AC versus PC ($N = 2$) [46,47], VAC versus PC ($N = 1$) [17], GC versus AC ($N = 1$) [52], VAC versus GC ($N = 1$) [53], and VGC versus VAC ($N = 1$) [55], see Fig. S11. All antiviral agents were not significantly different in composite major adverse effects relative to PC, see Table 2. Comparison adjusted funnel plots were asymmetric, which suggested some missing publications, see Fig. S12. There was no evidence of inconsistency (Chi-square = 0.05, *P*-value 0.828).

### Treatment ranking

The cumulative ranking probability and SUCRA methods were applied to assess the best treatment in lowering overall CMV infections, which identified VGC, GC, and VAC as the three highest ranked treatments with SUCRAs of 92.0, 77.5, and 55.3, accordingly, see Table S10. For CMV disease, the three highest ranked treatments were VGC, VAC, and GC. The SUCRAs for these corresponding values were 90.5, 66.3, and 61.7, see Table S10. For D+/R− patients, VGC was ranked as the first, followed by GC and VAC with the SUCRAs of 85.0, 74.0, and 51.2. For composite major adverse effects, VGC, VAC, GC, and AC results were distinguished as the best in safety (i.e., lowering adverse effects) with the SUCRAs of 6.3, 47.0, 61.8, and 84.5, respectively, see Table S11.

A cluster plot was simultaneously constructed based on benefits and safety outcomes by plotting SUCRAs of CMV infection/disease on the *x*-axis and safety on the *y*-axis, in which a higher *x*-value is preferred whereas a higher *y*-value is less preferred treatment. A plot is equally divided into quarters at the midpoint for both axes, and if the treatment fell in the far-right *x*-axis and the lowest *y*-axis that indicated the highest benefit with the lowest adverse drug reaction, see Fig. 2. The VGC treatment fell in the right lower quadrant, from which it could be interpreted that it has high benefit in the prevention of CMV infection/ disease with lowest risks of major adverse drug reaction. GC fell in the right upper quadrant indicating moderate benefit with moderate risk whereas the VAC gave a lower benefit with lower major adverse drug reactions.

### Risk-benefit analysis

Monte Carlo simulation was used to appraise risks from major adverse drug reaction and benefits of infection/ disease prevention, see Table S12. Probabilistic sensitivity analysis was plotted into four quadrants of the incremental risk-benefit plane. Each quadrant indicates the risk and benefit as follows: the right-upper quadrant (QI) referred to high risk (adverse effect) with high benefit, left-upper quadrant (QII) referred to high risk with low benefit, left-lower quadrant (QIII) referred to less benefit and low risk, and right-lower quadrant (QIV) referred to high benefit and low risk, see Fig. 3. Two clinical thresholds (0.2 and 0.3) were used for trading off incremental risks, and incremental benefits, i.e., out of 10 patients who benefit as free from CMV infection, 2 and 3 patients would experience adverse drug reaction from the prophylaxis. Results showed that VGC was in the QIV and being in the far-left *x*-axis indicated the lowest risk and highest benefit. GC fell in the Q1 indicating benefit but still had moderate risk whereas VAC fell in the Q1 but lower *x*-values than GC indicating lower risk and benefit than GC. However, these agents all showed greater benefits (incremental benefit ranging from 0.5 to 0.8), but some adverse drug reactions could not be avoided. However, all these treatments were almost acceptable under these thresholds, see Fig. 3. A net clinical benefit curve was constructed by weighting the treatment benefit in preventing CMV infection against composite major adverse effects of five possible comparison pairs; VGC, VAC, GC compared to PC, VGC, and VAC compared to GC according to various clinical thresholds, see Fig. 4. The clinical threshold is a value of acceptable risk from 0 (risk of adverse effects from medication are not acceptable at all) to 1 (risk is acceptable even if all patients have adverse effects). Compared to PC, VGC and VAC had higher positive net benefit than GC only if the clinical threshold was <0.3.

## Discussion

We conducted SM-NMA to simultaneously investigate the efficacy and safety of anti-CMV prophylaxis of CMV in KT. Our findings suggested that VGC was the most efficacious prophylactic agent, showing the highest SUCRAs for CMV infections as well as CMV disease, while adverse drug reactions were the lowest. Therefore, this result helped to confirm why many clinical practice guidelines have recommended VGC as the first-line drug for prophylaxis of CMV in solid organ transplant including KT [15,16]. Our findings were largely similar to previous meta-analyses and only differed for AC, which was reported to offer 55% lower CMV disease in solid organ transplantation compared to PC [25,26,62]. We did not identify any benefit of AC in the prevention of either early/late CMV infection and CMV disease

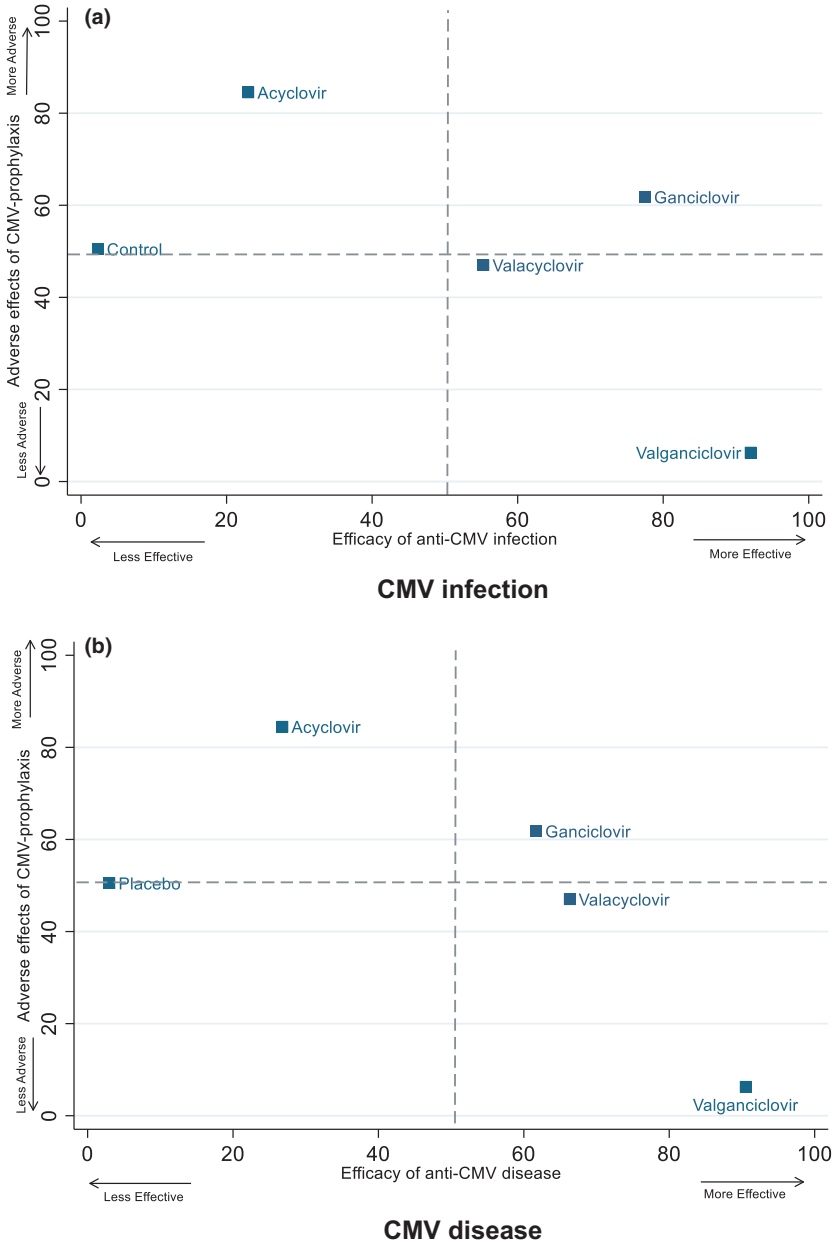


**Figure 2** Cluster plots of SUCRA values of efficacy in lowering CMV infection (a) and disease (b) versus adverse drug reactions from anti-CMV prophylaxis. *X*-axis is SUCRA of efficacy in preventing CMV and *y*-axis is SUCRA of major adverse drug reaction (neutropenia, thrombocytopenia, leucopenia, anemia, and hallucination). Higher *X* value reflects higher benefit whereas higher *Y*-value reflects higher major adverse drug reaction or less benefit of treatment.

following KT. This inconsistency may reflect differences in the assessment of all solid organ transplants in comparison to KTs alone. Their pharmacokinetics can partly explain the efficacy of different antiviral agents. Whilst, AC has been reported to offer limited absorption with very low bioavailability (10–17%) [63] compared to VAC which is a L-valyl ester of acyclovir but has a very high level of bioavailability approximately 55% [64].

From the cluster ranking plot in this study, it was also distinguished that AC was associated with the highest risk of major adverse effects. In practice, patients would require antiviral agents in the long term to limit the effect of CMV infection/disease along with immunosuppressive agents after transplantation, thus safety is mandatory to be considered. Currently, AC is not recommended for prophylaxis of CMV because of its less efficacy and highest side effects. From the DMA result in pre-emptive treatment, GC could lower the incidence of CMV disease by approximately 33.0%, while the efficacy of GC in the prophylaxis regimen was around 26%. GC has been used intravenously for the prevention and treatment of CMV infection/disease [65–67], but this may not be convenient for long term use (90–180 days per prophylaxis period) because of repeated

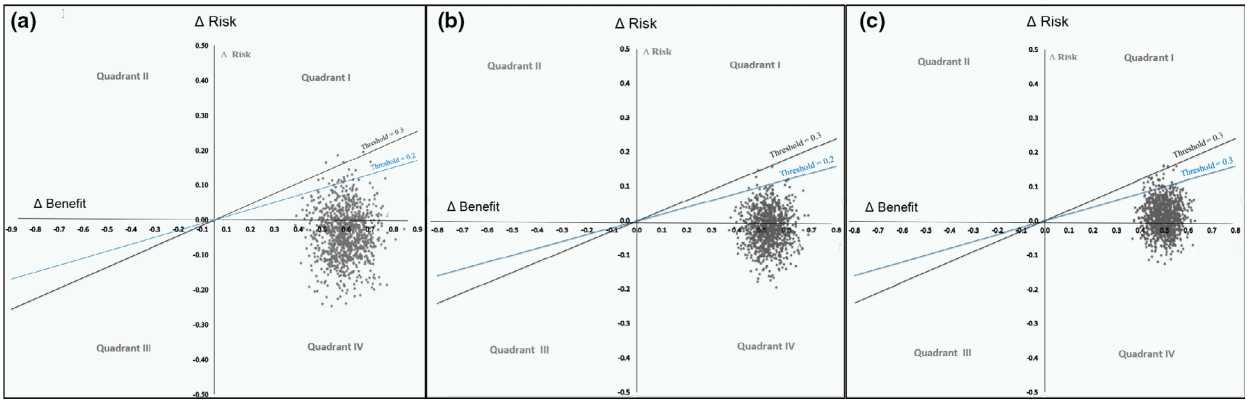


**Figure 3** Risk-benefit plane curve of lowering CMV infection versus adverse effects for antiviral agents versus placebo. (a) Comparison of VGC versus control. (b) Comparison of VAC versus control. (c) Comparison of GC versus control.

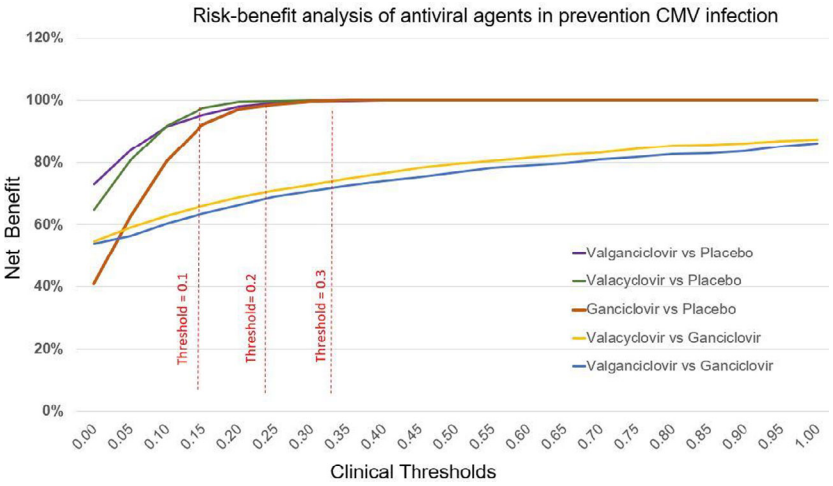


**Figure 4** Comparison between acceptable clinical threshold and percent of Net Benefit CMV prophylaxis.

hospital visits for intravenous administration and the risk of infection associated with catheterisation [68]. VGC is a prodrug of GC, and the absolute bioavailability is very high, up to approximately 60% [69,70]. The comparative efficacy of these antiviral agents may ultimately be because of their serum concentrations, which concurs with our findings. Nonetheless, VAC might be considered as the second line treatment in developing countries, where VGC and GC accessibility are limited regardless of CMV seropositive or seronegative recipients. For high-risk situations, such as D+/R− or in patients receiving induction therapy with lymphocyte depleting agent or ATG, our review indicated that VAC could not prevent CMV infection/disease. Therefore, the selection of anti-CMV agents in these patients should be either VGC or GC, while VAC or AC are not recommended. Further economic evaluation studies should be ascertained whether VGC is cost-effective relative to VAC [24]. However, the weakness of implementing VAC instead of VGC is the requirement of a very high dose of 8000 mg/day or 2000 mg four times a day, which could decrease compliance because of the burden of administration.

To our knowledge, this is the first study considering all available antiviral agents in the prevention of early and late-phase CMV infection, see Table S13. Additionally, we also considered the adverse effects of the treatments for long term use. Furthermore, the incremental risks and benefits of CMV prophylaxis were weighed accordingly using a cluster plot and using reasonable clinical thresholds. However, we could not avoid some limitations in the analysis part, as there are some heterogeneities from the difference between doses, administration route of GC (oral vs IV), and duration of prophylaxis which varied from 1 to 6 months, and CMV serologies (D+/R+, D−/R+, D+/R−, and D−/R−)

which leads to uncertainty. Although oral GC is not currently available to any further extent in current practice, we found a potential benefit of GC even though most studies were conducted on oral forms. Thus, we predict that IV GC may be more efficacious than oral GC because of higher bioavailability and serum concentration under therapeutic dose [71–73].

Superimposed viral or bacterial infections are also of interest, but are only reported in a small number of studies. The paramount adverse impact on CMV infection after KT is considered as a potential harm factor for acute allograft rejection [74,75]. CMV can indirectly cause dysregulation in the immune system by increasing the amount of inflammatory cytokine which could augment the immune response, which would accelerate the collagen synthesis in allograft and might participate in the risk of renal acute graft rejection [76,77]. Therefore, anti-CMV prophylaxis is a new challenge associated with the protection of acute allograft dysfunction after KT. Future studies, should further pool the effect of antiviral agents to prevent acute allograft rejection.

## Conclusion

Valganciclovir is the most efficacious and safest in the prophylaxis of CMV infection and disease after KT, follow by GC in general and high-risk patients with D+/R−. VAC might be an alternative for general, but not for high-risk patients with D+/R− where VGC and GC are not available. Further economic evaluation to assess the cost-effectiveness of VGC in comparison to GC should be considered.

## Authorship

Narisa Ruenroengbun participated in research design, writing paper, the performance of the research, and data analysis. Pawin Numthavaj participated in research design, editing paper, the performance of the research, and data analysis. Tunlanut Sapankaew participated in the performance of the research. Kamolpat Chaiyakittusopon participated in the performance of the research. Atiporn Ingsathit participated in research design and contributed to the clinician aspect. Gareth J Mckay participated in performance of the research and writing paper. John Attia participated in the performance of the research and writing paper. Ammarin Thakkinstian participated in research design, writing paper, the performance of the research, and data analysis.

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## Conflicts of interest

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Search strategy using a PICO framework.

**Table S2.** Summary of excluded studies.

**Table S3.** Definition for CMV disease diagnosis and infection.

**Table S4.** Summary of events used in network meta-analysis in prophylaxis and pre-emptive strategy.

**Table S5.** Risk of bias assessment for 24 included studies from RoB.

**Table S6.** Summarized risk of bias assessment for five domains and overall bias.

**Table S7.** Estimation of relative treatment effects of anti-CMV prophylaxis antiviral agents on CMV infection and CMV disease outcomes.

**Table S8.** Estimation of relative treatment effects of anti-CMV prophylactic antiviral agents on early-onset and late-phase CMV infection.

**Table S9.** Estimation of relative treatment effects in CMV prophylaxis in high-risk patients with D+/R− with/without induction therapy of lymphocyte-depleting agent or anti-thymocyte globulin.

**Table S10.** SUCRA and best prevention probability for anti-CMV prophylaxis antiviral agents in reduced CMV infection and CMV disease.

**Table S11.** SUCRA and best safety probability for lowering composite major adverse drug reaction with anti-CMV prophylaxis.

**Table S12.** Probabilistic sensitivity analysis parameters.

**Table S13.** Summary of published systematic reviews and meta-analyses for prevention of CMV disease or infection in transplantation.

**Figure S1.** Forest plot of anti-CMV prophylaxis on CMV infection in direct meta-analysis.

**Figure S2.** Network map of prophylaxis antiviral agents for CMV infection.

**Figure S3.** Network map of prophylaxis antiviral agents for early onset (≤6 months) and late phase (>6 months–4 years) CMV infection.

**Figure S4.** Comparison adjusted funnel plots of anti-CMV prophylaxis.

**Figure S5.** Comparison adjusted funnel plots of early onset (≤6 m) and late-phase (>6 months–4 years) CMV infection.

**Figure S6.** Network map of subgroup analysis of anti-CMV prophylaxis antiviral agents in high-risk of CMV.

**Figure S7.** Forest plot of anti-CMV prophylaxis on CMV disease in direct meta-analysis.

**Figure S8.** Network map of prophylaxis antiviral agents for CMV disease.

**Figure S9.** Comparison adjusted funnel plots of prophylaxis CMV disease.

**Figure S10.** Forest plot of pre-emptive CMV disease in direct meta-analysis.

**Figure S11.** Network map of prophylaxis antiviral agents for composite major adverse drug reaction.

**Figure S12.** Comparison adjusted funnel plots of composite major adverse drug reaction.

## REFERENCES


1. Transplantation World Health Organization. Transplantation World Health Organization (WHO) annual report. Geneva: Transplantation World Health Organization, 2019. Available from: https://www.who.int/transplantation/gkt/statistics/en/.
2. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012; **7**: 2058.
3. Hasanzamani B, Hami M, Zolfaghari V, Torkamani M, Ghorban Sabagh M, Ahmadi SS. The effect of cytomegalovirus infection on acute rejection in kidney transplanted patients. *J Renal Inj Prev* 2016; **5**: 85.
4. Couchoud C. Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation. *Cochrane Database Syst Rev* 2000; (2): CD001320.
5. Sagedal S, Nordal KP, Hartmann A, *et al*. The impact of cytomegalovirus infection and disease on rejection episodes in renal allograft recipients. *Am J Transplant* 2002; **2**: 850.
6. Azevedo P, Freitas C, Aguiar P, *et al*. Cytomegalovirus pneumonia ten years after renal transplant – a manifestation of sustained lymphocyte depletion. Internet. *J Infect Dis* 2014; **13**.
7. Humar A, Mazzulli T, Moussa G, *et al*. Clinical utility of cytomegalovirus (CMV) serology testing in high-risk CMV D+/R− transplant recipients. *Am J Transplant* 2005; **5**: 1065.
8. Rawal BB, Shadrou S, Abubacker F, Ghahramani N. A systematic review and meta-analysis of prophylactic versus pre-emptive strategies for preventing cytomegalovirus infection in renal transplant recipients. *Int J Organ Transplant Med* 2012; **3**: 10.
9. Weikert BC, Blumberg EA. Viral infection after renal transplantation: surveillance and management. *Clin J Am Soc Nephrol* 2008;**3**(Suppl 2); S76.
10. Alberú J, Morales-Buenrostro LE, Correa-Rotter R, *et al*. Long-term renal graft function and survival in patients with high-risk for cytomegalovirus infection receiving preemptive therapy. *Rev Invest Clin* 2008; **60**: 365.
11. Alexopoulos SP, Lindberg L, Subramanyan RK, Matsuoka L. Cytomegalovirus prophylaxis in solid organ transplantation. *Curr Med Chem* 2012; **19**: 5957.
12. Reischig T, Jindra P, Hes O, Švecová M, Klaboch J, Třeška V. Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. *Am J Transplant* 2008; **8**: 69.
13. Kacer M, Kielberger L, Bouda M, Reischig T. Valganciclovir versus valacyclovir prophylaxis for prevention of cytomegalovirus: an economic perspective. *Transplant Infect Dis* 2015; **17**: 334.
14. Abu-Nader R, Patel R. Current management strategies for the treatment and prevention of cytomegalovirus infection in solid organ transplant recipients. *BioDrugs* 2000; **13**: 159.
15. Kotton CN. Migrating from universal to personalized prevention: predicting the risk of cytomegalovirus infection after organ transplantation. *Transplantation* 2018; **102**: 1787.
16. Kasiske BL, Zeier MG, Chapman JR, *et al*. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int* 2010; **77**: 299.
17. Lowance D, Neumayer H-H, Legendre CM, *et al*. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med* 1999; **340**: 1462.
18. Ahmed A. Antiviral treatment of cytomegalovirus infection. *Infect Disord Drug Targets* 2011; **11**: 475.
19. Bruminhent J, Bushyakanist A, Kantachuvesiri S, Kiertiburanakul S. A nationwide survey of cytomegalovirus prevention strategies in kidney transplant recipients in a resource-limited setting. open forum. *Infect Dis* 2019; **6**: ofz322-ofz.
20. Bruminhent J, Dajsakdipon T, Ingsathit A, Supaporn T, Prommool S, Watcharananan SP. Impact of cytomegalovirus serostatus on allograft loss and mortality within the first year after kidney transplantation: an analysis of the national transplant registry. *Transpl Proc* 2020; **52**: 829.
21. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood* 2009; **113**: 5711.

22. Rezzouk B, Bouattar T, Belkadi B, *et al*. Current characteristics and outcomes of Cytomegalovirus Reactivation in kidney transplant seropositive recipients in the era of prophylaxis treatment. Lesson from single Moroccan center experience. *medRxiv* 2019: 19001008.
23. Rezzouk B, Bouattar T, Belkadi B, *et al*. Characteristics and outcomes of cytomegalovirus infection in seropositive kidney transplant recipients in the era of antiviral prophylaxis with valacyclovir: a single-center study in Morocco. *Transplant Res Risk Manage* 2021; **13**: 1.
24. Kielberger L, Bouda M, Jindra P, Reischig T. Pharmacoeconomic impact of different regimens to prevent cytomegalovirus infection in renal transplant recipients. *Kidney Blood Press Res* 2012; **35**: 407.
25. Hodson EM, Craig JC, Strippoli GFM, Webster AC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev* 2008; (2): CD003774.
26. Hodson EM, Ladhani M, Webster AC, Strippoli GFM, Craig JC. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev* 2013; (2): CD003774.
27. Hwang SD, Lee JH, Lee SW, Kim JK, Kim MJ, Song JH. Effect of low-dose vs standard-dose valganciclovir in the prevention of cytomegalovirus disease in kidney transplantation recipients: a systemic review and meta-analysis. *Transpl Proc* 2018; **50**: 2473.
28. Caskurlu H, Karadag FY, Arslan F, Cag Y, Vahaboglu H. Comparison of universal prophylaxis and preemptive approach for cytomegalovirus associated outcome measures in renal transplant patients: a meta-analysis of available data. *Transplant Infect Dis* 2019; **21**: e13016.
29. Vaziri S, Pezhman Z, Sayyad B, *et al*. Efficacy of valganciclovir and ganciclovir for cytomegalovirus disease in solid organ transplants: a meta-analysis. *J Res Med Sci* 2014; **19**: 1185.
30. Zhang Y, Zhou T, Huang M, Gu G, Xia Q. Prevention of cytomegalovirus infection after solid organ transplantation: a Bayesian network analysis. *Ann Clin Microbiol Antimicrob* 2020; **19**: 34.
31. Andrews PA, Emery VC, Newstead C. Summary of the British transplantation society guidelines for the prevention and management of CMV disease after solid organ transplantation. *Transplantation* 2011; **92**: 1181.
32. Kotton CN, Kumar D, Caliendo AM, *et al*. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013; **96**: 333.
33. Ljungman P, Boeckh M, Hirsch HH, *et al*. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis* 2017; **64**: 87.
34. Marin F, Rohatgi A, Charlot S. WebPlotDigitizer, a polyvalent and free software to extract spectra from old astronomical publications: application to ultraviolet spectropolarimetry, 2017. Available from https://automeris.io/WebPlotDigitizer.
35. Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
36. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008; **61**: 991.
37. Meta-analyses SP. How to read a funnel plot. *BMJ* 2013; **346**: f1342.
38. Palmer TM, Peters JL, Sutton AJ, Moreno SG. Contour-enhanced funnel plots for meta-analysis. *Stata J* 2008; **8**: 242.
39. Conti DJ, Shen G, Singh T, Isenberg A, Freed BM. Ganciclovir prophylaxis of cytomegalovirus disease. *Transpl Proc* 1997; **29**: 804.
40. Conti DJ, Freed BM, Gruber SA, Lempert N. Prophylaxis of primary cytomegalovirus disease in renal transplant recipients: a trial of ganciclovir vs immunoglobulin. *Arch Surg* 1994; **129**: 443.
41. Conti DJ, Freed BM, Singh TP, Gallichio M, Gruber SA, Lempert N. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplants recipients. *Arch Surg* 1995; **130**: 1217; discussion 21–2.
42. Brennan DC, Garlock KA, Singer GG, *et al*. Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients. *Transplantation* 1997; **64**: 1843.
43. Rondeau E, Bourgeon B, Peraldi MN, *et al*. Effect of prophylactic ganciclovir on cytomegalovirus infection in renal transplant recipients. *Nephrol Dial Transplant* 1993; **8**: 858.
44. Ahsan N, Holman MJ, Sonderbye L, Langhoff E, Yang HC. Oral ganciclovir in the prevention of cytomegalovirus infection in postkidney transplant "CMV at risk" recipients: a controlled, comparative study of two regimens (750 mg Bid and 500 mg Bid). *Transpl Proc* 1998; **30**: 1383.
45. Leray H, Mourad G, Chong G, Segondy M, Mion C. Prophylactic treatment of cytomegalovirus primary infection with ganciclovir in renal transplant recipients. *Transpl Proc* 1995; **27**: 2448.
46. Pettersson E, Hovi T, Ahonen J, *et al*. Prophylactic oral acyclovir after renal transplantation. *Transplantation* 1985; **39**: 279.
47. Balfour HH Jr, Chace BA, Stapleton JT, Simmons RL, Fryd DS. A randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. *N Engl J Med* 1989; **320**: 1381.
48. Kletzmayr J, Kotzmann H, Popow-Kraupp T, Kovarik J, Klauser R. Impact of high-dose oral acyclovir prophylaxis on cytomegalovirus (CMV) disease in CMV high-risk renal transplant recipients. *J Am Soc Nephrol* 1996; **7**: 325.
49. Rostaing L, Crespin A, Icart J, *et al*. Cytomegalovirus (CMV) prophylaxis by acyclovir in pre-transplant CMV-positive renal transplant recipients. *Transplant Int* 1994; **7**(Suppl 1): S331.
50. Jiang J, Zhu Y, Jian G, Zhu W. Randomized case-controlled trial of oral low-dose acyclovir for prevention of virus infections in recipients of renal allografts. *Chin Med J* 1995; **108**: 459.
51. Flechner SM, Avery RK, Fisher R, *et al*. A randomized prospective controlled trial of oral acyclovir versus oral ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998; **66**: 1682.
52. Rubin RH, Kemmerly SA, Conti D, *et al*. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transplant Infect Dis* 2000; **2**: 112.
53. Reischig T, Opatrný K Jr, Třeška V, Mareš J, Jindra P, Švecová M. Prospective comparison of valacyclovir and oral ganciclovir for prevention of cytomegalovirus disease in high-risk renal transplant recipients. *Kidney Blood Press Res* 2005; **28**: 218.
54. Pavlopoulou ID, Syriopoulou VPH, Chelioti H, *et al*. A comparative randomised study of valacyclovir vs. oral ganciclovir for cytomegalovirus prophylaxis in renal transplant recipients. *Clin Microbiol Infect* 2005; **11**: 736.
55. Reischig T, Kacer M, Hruba P, *et al*. Less renal allograft fibrosis with valganciclovir prophylaxis for cytomegalovirus compared to high-dose valacyclovir: a parallel group, open-

label, randomized controlled trial 11 medical and health sciences 1103 clinical sciences. *BMC Infect Dis* 2018; **18**: 573.
56. Paya C, Humar A, Dominguez ED, *et al*. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4**: 611.
57. Brennan DC, Garlock KA, Lippmann BA, *et al*. Control of cytomegalovirus-associated morbidity in renal transplant patients using intensive monitoring and either preemptive or deferred therapy. *J Am Soc Nephrol* 1997; **8**: 118.
58. Yang CW, Kim YO, Kim YS, *et al*. Clinical course of cytomegalovirus (CMV) viremia with and without ganciclovir treatment in CMV-seropositive kidney transplant recipients. Longitudinal follow-up of CMV pp65 antigenemia assay. *Am J Nephrol* 1998; **18**: 373.
59. Hibberd PL, Tolkoff-Rubin NE, Conti D, *et al*. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. *Ann Intern Med* 1995; **123**: 18.
60. Koetz AC, Delbrück R, Furtw??ngler A, *et al*. Cytomegalovirus pp65 antigen-guided preemptive therapy with ganciclovir in solid organ transplant recipients: a prospective, double-blind, placebo-controlled study. *Transplantation* 2001; **72**: 1325.
61. Sagedal S, Nordal KP, Hartmann A, *et al*. Pre-emptive therapy of CMVpp65 antigen positive renal transplant recipients with oral ganciclovir: a randomized, comparative study. *Nephrol Dial Transplant* 2003; **18**: 1899.
62. Hodson EM, Jones CA, Webster AC, *et al*. Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials. *Lancet* 2005; **365**: 2105.
63. Lewis LD, Fowle AS, Bittiner SB, Bye A, Isaacs PE. Human gastrointestinal absorption of acyclovir from tablet duodenal infusion and sipped solution. *Br J Clin Pharmacol* 1986; **21**: 459.
64. Tyring SK, Baker D, Snowden W. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. *J Infect Dis* 2002; **186**(Supplement_1): S40.
65. Brennan DC, Storch GA, Lippman BJ. Preemptive ganciclovir therapy in renal transplantation. *Ann Intern Med* 1996; **124**: 693.
66. Said T, Nampoory M, Johny KV, *et al*. Cytomegalovirus prophylaxis with ganciclovir in kidney transplant recipients receiving induction antilymphocyte antibodies. *Transpl Proc* 2004; **36**: 1847.
67. Said T, Nampoory M, Pacsa AS, *et al*. Oral valgancyclovir versus intravenous gancyclovir for cytomegalovirus prophylaxis in kidney transplant recipients. *Transpl Proc* 2007; **39**: 997.
68. Handisurya I, Risan N, Prasetyo DWI. Side effects of intravenous ganciclovir and combination of intravenous ganciclovir-oral valganciclovir in pediatric patients with cytomegalovirus infection. *Asian J Pharm Clin Res* 2019; **12**: 68.
69. Pescovitz MD, Bumgardner G, Gaston RS, *et al*. Pharmacokinetics of daclizumab and mycophenolate mofetil with cyclosporin and steroids in renal transplantation. *Clin Transplant* 2003; **17**: 511.
70. Brown F, Banken L, Saywell K, Arum I. Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers. *Clin Pharmacokinet* 1999; **37**: 167.
71. Anderson RD, Griffy KG, Jung D, Dorr A, Hulse JD, Smith RB. Ganciclovir absolute bioavailability and steady-state pharmacokinetics after oral administration of two 3000-mg/d dosing regimens in human immunodeficiency virus- and cytomegalovirus-seropositive patients. *Clin Ther* 1995; **17**: 425.
72. Winston DJ, Busuttil RW. Randomized controlled trial of sequential intravenous and oral ganciclovir versus prolonged intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in high-risk cytomegalovirus-seronegative liver transplant recipients with cytomegalovirus-seropositive donors. *Transplantation* 2004; **77**: 305.
73. Nafar M, Pezeshki ML, Farrokhi F, *et al*. A Randomized prospective trial of oral versus intravenous ganciclovir for prophylaxis of cytomegalovirus infection and disease in high-risk kidney recipients. *Transpl Proc* 2005; **37**: 3053.
74. Reischig T, Jindra P, Švecová M, Kormunda S, Opatrný K Jr, Třeška V. The impact of cytomegalovirus disease and asymptomatic infection on acute renal allograft rejection. *J Clin Virol* 2006; **36**: 146.
75. Basadonna G, Feria A, Perez R, Klein H, Sturges M, Colquhoun S. Incidence of infection and acute rejection after cytomegalovirus immune globulin prophylaxis in renal transplantation. *Transpl Proc* 1994; **26**(5 Suppl 1): 52.
76. Freedman SR, Ravichandran BR, Masters BM, *et al*. Clinical outcomes of valganciclovir prophylaxis in high-risk (D+/R−) renal transplant recipients experiencing delayed graft function. *Transplant Infect Dis* 2019; **21**: e13125.
77. Freeman RB Jr. The 'indirect' effects of cytomegalovirus infection. *Am J Transplant* 2009; **9**: 2453.