

# A Nationwide Survey of Cytomegalovirus Prevention Strategies in Kidney Transplant Recipients in a Resource-Limited Setting

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**Objective.** Strategies to prevent cytomegalovirus (CMV) infection in resource-limited settings have been under-explored. We investigated CMV prevention strategies utilized among transplant centers in Thailand.

**Method.** A questionnaire on CMV prevention strategies for kidney transplant (KT) recipients was developed using a web-based electronic survey website ([www.surveymonkey.com](http://www.surveymonkey.com)). The survey was delivered to 31 transplant centers in Thailand. One infectious disease physician (ID) and 1 nephrologist (NP) from each center were included.

**Results.** There were 43 respondents from 26 of the 31 transplant centers (84%), including 26 (60%) IDs and 17 (40%) NPs. Forty-one (95%) (41/43) physicians agreed on the necessity of CMV prevention. Of these, 77% (33/43) physicians implemented prevention strategies for their patients. Interventions included preemptive approaches (48%), prophylaxis (45%), hybrid approaches; surveillance after prophylaxis (3%), and CMV-specific immunity-guided approaches (3%). For CMV-seropositive KT recipients, use of preemptive approaches (84%) exceeded prophylaxis (12%). However, 81% of the former preferred targeted prophylaxis in patients receiving antithymocyte globulin therapy. Sixty-five percent and 93% of physicians started preemptive therapy when plasma CMV DNA loads reached 2000 and 3000 copies/mL (1820 and 2730 IU/mL), respectively. A significantly greater percentage of NPs initiated preemptive therapy at a plasma CMV DNA load of 1820 IU/mL compared with IDs (88% vs 50%;  $P = .02$ ). The most common barrier to prevention strategy implementation was financial inaccessibility of oral valganciclovir (67%) and quantitative CMV DNA testing (12%).

**Conclusions.** Most physicians agreed on a need for preemptive approaches, although prophylaxis was targeted in those receiving intense immunosuppression. The financial implication is the main barrier for CMV prevention in Thailand.

**Key words:** burden; cytomegalovirus; cut-off; hybrid approach; preemptive therapy; prophylaxis; threshold; viral load.

## INTRODUCTION

Cytomegalovirus (CMV) is a re-emerging human herpes virus, which causes substantial morbidity and occasional mortality in immunocompromised patients [1]. Among these, solid organ transplant recipients who maintain an allograft by receiving immunosuppressive drugs are well-known to be at risk of infection. CMV infection after kidney transplantation (KT) reportedly ranges from asymptomatic infection to symptomatic

CMV syndrome and tissue-invasive disease [2]. Data from 2 retrospective studies in Thailand revealed the prevalence of CMV seropositivity in both donors and recipients was 99 percent. Despite preexisting immunity in most patients indicated by CMV seropositivity, they remain at moderate risk of CMV infection. The prevalence of asymptomatic CMV infection and CMV disease in KT recipients were 5%–21% and 7%, respectively. Risk factors include advanced age of the recipient and use of antithymocyte globulin (ATG) for induction or steroid-resistant rejection therapy [3, 4]. Patients developing CMV diseases carry a greater risk of allograft failure and death compared with those free from CMV disease [3]. Furthermore, KT recipients who developed drug-resistant CMV infection could suffer increased morbidity from prolonged CMV DNAemia and anti-CMV therapy [5]. Prevention of this infection remains a suitable intervention to limit unfavorable consequences. Two international guidelines from the Transplantation Society and the American Society of Transplantation Infectious Disease Community of Practice encouraged implementation of prevention strategies for CMV infection among KT recipients [6,

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7]. Although the guideline for prevention of CMV infection in Thai KT care was developed by the Thai Transplant Society, the strategies implemented among transplant centers in Thailand remained variable [8]. Despite the fact that a preemptive approach is recommended in CMV-seropositive KT recipients by the aforementioned guideline, impracticability and financial restrictions could limit its utilization in real-world practice. Additionally, an optimal cut-off value of plasma CMV DNA load has not been standardized among physicians. Furthermore, an investigation of real-life strategies to prevent this specific infection has never been performed, especially in resource-limited settings. Therefore, we aimed to investigate CMV prevention strategies utilized among transplant centers in Thailand. We also investigated differing perspectives in terms of CMV prevention in KT recipients between infectious disease physicians (ID) and nephrologists (NP).

## METHODS

### Questionnaire

A survey was delivered to all 31 transplant centers in Thailand during October and November 2018. One ID and 1 NP, who were directly caring for KT recipients at each transplant center, were included. The names of the transplant centers and physicians were obtained from the Thai Transplant Society in October 2018. An email with a link to the electronic survey was sent to all physicians with a reminder email if a response was not received. The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

A questionnaire on CMV prevention strategies for KT recipients was developed using a web-based electronic survey website ([www.surveymonkey.com](http://www.surveymonkey.com)). The survey included the respondents' demographic data, such as sex, age, transplant center setting or years in KT practice, and CMV prevention strategies. CMV prevention strategies were defined according to the recently published guidelines [6, 7]. Prophylaxis was defined as administration of anti-CMV drugs, either intravenous (IV) ganciclovir or oral valganciclovir, for a defined period of time after KT. A preemptive approach was defined as surveillance of plasma CMV DNA load, quantified by real-time polymerase chain reaction (PCR) assay and initiation of anti-CMV drugs when the cut-off value was reached to prevent progression from asymptomatic CMV infection to disease. Plasma CMV DNA load was reported in both copies/mL and international units (IU)/mL, based on the use of a quantitative real-time PCR technique by COBAS AmpliPrep/COBAS TaqMan (TaqMan CMV Test, Roche Molecular Diagnostics, Branchburg, NJ). One copy/mL was calibrated to 0.91 IU/mL by the calibration of tests with the World Health Organization international standard [9]. Targeted prophylaxis or preemptive approaches were defined as above, but they were focused on a defined high-risk group of patients rather than universal implementation. A hybrid

approach was defined as surveillance by plasma CMV DNA quantification after cessation of a defined period of prophylaxis. A CMV-specific immunity-guided approach was defined as an intervention (prophylaxis, preemptive approach, or closed observation) guided by measurement of cell-mediated immunity, such as CMV-specific T-cell immunity assay.

### Statistical Analyses

Demographic data of all physicians involved in the study were analyzed by descriptive analysis. Categorical data were described as frequencies and percentages and compared by Fisher exact test. A  $P$  value  $< .05$  was considered statistically significant. Statistical analyses were performed with the statistical software Stata version 15 (StataCorp, LLC, College Station, TX).

## RESULTS

### Demographic Data

There were 43 respondents from 26 of the 31 (84%) transplant centers, including 26 (60%) IDs and 17 (40%) NPs. The demographic data of all physicians included in the survey are summarized in [Table 1](#). Fifty-eight percent of respondents were aged 35–44 years and approximately half were males (49%). Two-thirds of the physicians had been working in a public hospital setting (63%) and encountering KT recipients for at least 2 years (74%). The demographic data between the ID and NP groups were comparable; however, there were slightly more male physicians among the IDs compared with the NP group (62% vs 29%;  $P = .06$ ). There were also significantly more physicians from a public hospital setting in the ID group compared with the NP group (81% vs 36%;  $P < .05$ ).

### CMV Prevention Strategies

Overall responses in terms of CMV prevention strategies and the different perspectives between the ID and NP groups are shown in [Figure 1](#). Forty-one (95%) physicians agreed with a need for CMV prevention in KT recipients, although 33 physicians (77%) stated that they already utilized prevention strategies for their patients. Cytomegalovirus prevention strategies currently implemented include preemptive approaches (48%), universal prophylaxis (45%) (either by IV ganciclovir or oral valganciclovir), hybrid approaches; surveillance after prophylaxis (3%), and CMV-specific immunity-guided approach (3%). When specifically asked about the potential role of CMV prevention in Thai KT recipients, when the majority are CMV seropositive and likely to receive an allograft from a CMV seropositive donor, only 5% of physicians stated no need for prevention in this scenario. The remaining 95% reported that they preferred the preemptive approach (84%) over prophylaxis (12%). However, 81% of the former preferred targeted prophylaxis for those receiving ATG.

Among physicians choosing to implement prophylaxis, the duration of prophylaxis ranged from less than 1 to more than

**Table 1. Demographic Data of Infectious Disease Physicians and Nephrologists Who Participated in the Survey**

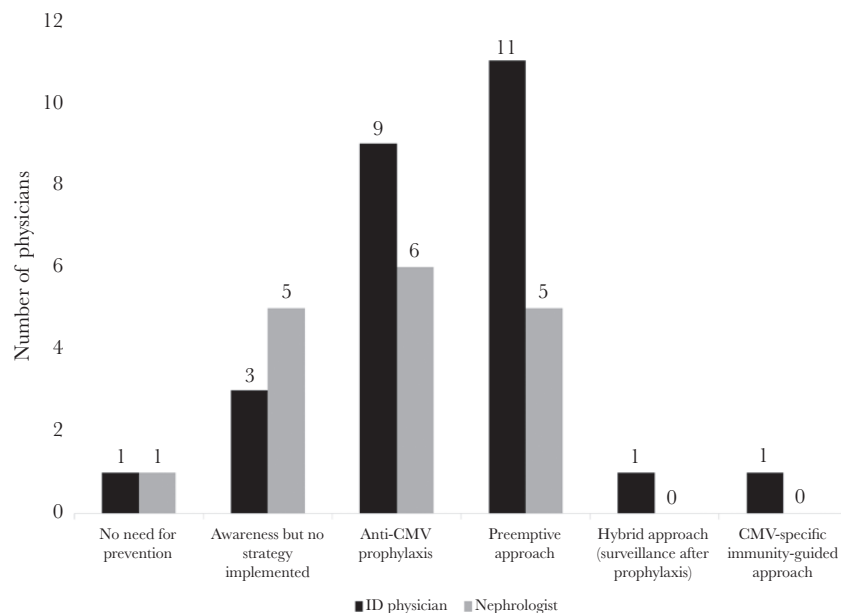
Characteristics	Infectious Disease Physicians (n = 26)	Nephrologists (n = 17)	P value
Male, n (%)	16 (62)	5 (29)	.06
Age, years, n (%)			
25–34	5 (19)	9 (53)	.04
35–44	18 (69)	7 (41)	.11
45–54	3 (12)	1 (6)	1.00
Transplant center setting, n (%)			
Public general hospital	10 (39)	2 (12)	.09
Public university hospital	11 (42)	4 (24)	.33
Nonprofit hospital	1 (4)	8 (47)	.001
Others	4 (15)	3 (17)	1.00
Years in kidney transplant recipients care, n (%)			
<1	3 (12)	2 (12)	1.00
1–2	1 (4)	5 (29)	.03
2–5	15 (57)	5 (29)	.12
5–10	4 (15)	3 (18)	1.00
>10	3 (12)	2 (12)	1.00

6 months, with half (51%) choosing to implement prophylaxis over a 3-month course. For the preemptive approach, 65% and 93% of all physicians initiated preemptive therapy when the plasma CMV DNA load reached 2000 and 3000 copies/mL (1820 and 2730 IU/mL) or 3.3 and 3.4 log<sub>10</sub> copies/mL (3.2 and 3.4 log<sub>10</sub> IU/mL), respectively [Figure 2](#). At a plasma CMV DNA load cut-off value of 5000 copies/mL (4550 IU/mL), almost all physicians (98%), either ID or NP, had initiated preemptive therapy for their patients. There was no difference in CMV prevention strategies between the 2 groups of physicians. A significantly greater percentage of

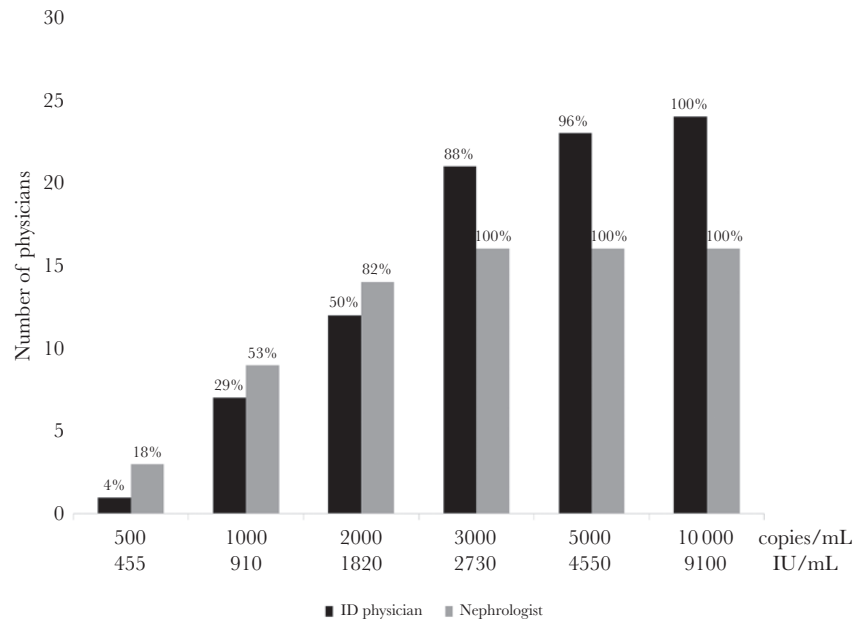
NPs initiated preemptive therapy at a plasma CMV load of 1820 IU/mL compared with IDs (88% vs 50%; *P* = .02).

**Barriers for CMV Prevention Strategies**

The most common barrier to implementation of CMV prevention strategies was inaccessibility to care, including financial incompatibility resulting in restricted access to oral valganciclovir and quantitative CMV DNA testing in 67% and 12% of the physicians, respectively. Lack of logistic support for plasma CMV DNA load measurement due to impracticability in real-life practice was reported in 16% of respondents. Side effect



**Figure 1.** Cytomegalovirus Prevention Strategies for Kidney Transplant Recipients in Thailand



**Figure 2.** Cumulative Numbers of Physicians Initiating Preemptive Therapy in Kidney Transplant Recipients with Varying Plasma Cytomegalovirus DNA Cut-off Values

intolerance of anti-CMV drug prophylaxis, especially bone marrow suppression from (val)ganciclovir, was reported in 5% of the physicians. Eighty-one percent felt that a guideline would enable physicians to more practically implement strategies for CMV prevention in their KT recipients. The remainder stated that greater self-education (14%) and transplant infectious disease consultation (5%) would be preferable.

## DISCUSSION

A nationwide survey of CMV prevention practice in both IDs and NPs was conducted with a response rate of greater than 80%. We report here the first survey of CMV prevention strategies for KT recipients in a resource-limited setting. The majority of respondents agreed there was a need for CMV prevention in this immunocompromised population although the approach is currently variable among physicians. The preemptive approach is the most common strategy utilized; however, prophylaxis is more favorable in patients receiving intense immunosuppression, such as ATG. We also demonstrated common CMV DNA cut-off values for initiation of preemptive therapy for Thai KT recipients. Financial incompatibility is the main inhibitory factor in a successful intervention. However, most respondents believe that practical guideline would encourage physicians to implement CMV preventive strategies in Thai KT recipients.

CMV has both direct and indirect effects in KT recipients. CMV disease, especially in those with allograft involvement, can cause significant morbidity. Allograft rejection, mortality, and opportunistic infection by infectious agents other than CMV are well-known consequences of CMV infection, which

could be explained by the modulation of the immune system by CMV itself [2]. In a resource-limited setting where the majority of adult KT recipients and donors are CMV seropositive, the risk of CMV infection after KT is considered to be moderate compared with western countries where CMV serostatus mismatches are common and pose a high risk. Data from previously cited studies in Thailand revealed prevention strategies are not universally utilized. A high rate of CMV disease in the period when quantitative CMV DNA testing is not practically available [3]. A relatively lower rate of CMV disease and some with asymptomatic CMV DNAemia, which would likely discover more from accessibility to PCR assay in the later years. In Thailand, financial constraints remain an issue regarding access to oral valganciclovir in an outpatient setting. In our center, patients receiving ATG for induction therapy received IV ganciclovir early posttransplant while being admitted to hospital and then later switched to a preemptive approach, forming a so-called hybrid approach. We also attempted to use this strategy in patients with steroid-resistant rejection requiring ATG; however, the rate of compliance remains uncertain. In our study, we have revealed that CMV prevention strategies are generally accepted, although the real-life implementation is not fully practiced. In general, implementation of the preemptive approach and anti-CMV prophylaxis are comparable. However, upon further investigation, we also report a preference for the preemptive approach among physicians treating CMV-seropositive KT recipients.

Of those treated preemptively, the optimal plasma CMV DNA cut-off value for initiation of therapy remains uncertain. Although the conversion of CMV DNA load from copies/mL to

IU/mL was recommended for implementation across all transplant centers, the recent international guidelines remain vague regarding the preemptive threshold. They recommended standardizing the cut-off value based on center-specific rates of CMV infection and clinical practices. Our survey revealed the applied threshold could range from 2000 to 3000 copies/mL (1820 and 2730 IU/mL). At least 90% of physicians initiated therapy when the plasma CMV DNA load reached 3000 copies/mL (2730 IU/mL), with almost all physicians initiating therapy by 5000 copies/mL (4550 IU/mL). Martín-Gandul and colleagues conducted a retrospective study to determine a valid threshold in plasma for preemptive therapy of CMV infection in CMV-seropositive solid organ transplant, including KT recipients. They found 3983 IU/ml (2600 copies/ml) to be the optimal cut-off for initiating preemptive therapy, with a high negative predictive value of 99.6% that could almost exclude CMV disease without specific anti-CMV therapy, particularly in those with moderate risk similar to our patients. This optimal cut-off value also showed sensitivity and specificity of 89.9% and 88.9%, respectively [10]. Our data reported a real-world plasma CMV DNA load threshold that encourages physicians to start preemptive therapy. We also found a trend of relatively early initiation of preemptive therapy in the NP group compared with the ID group. This could be explained by a greater percentage of patients being treated by NPs in a private setting where anti-CMV drug therapy is more available. However, dynamic monitoring of plasma CMV DNA load with the same clinical specimens and assays along with details of the clinical setting rather than single time-point interpretation is advised. The kinetics of CMV replication has been shown to be useful for the management of CMV infection in immunocompromised patients [11, 12]. Logistic support for measuring plasma CMV DNA load every week following transplantation is also not practical in our setting. A less frequent measurement, such as once every 2 weeks, in an outpatient clinic was commonly implemented in our practice. However, this strategy is not supported by Boillat Blanco et al, who revealed that less frequent monitoring may miss the opportunity to keep pace with the progression of the disease, especially in the postprophylaxis setting [13].

Among centers utilizing prophylaxis, either IV ganciclovir or oral valganciclovir was commonly used. Duration of prophylaxis was variable with the majority of courses ranging from 1 to 6 months. Although the preemptive approach is recommended in the guidelines for CMV-seropositive KT recipients, anti-CMV prophylaxis is also acceptable, though 3 months is the recommended duration. Only in CMV serostatus mismatch settings was an extension to 6 months after transplant mentioned. When we specifically investigated the intervention for CMV-seropositive KT recipients, more physicians tended to report a preemptive approach for their patients and individually considered those with high risk for anti-CMV prophylaxis. Targeted prophylaxis has been stated in the guidelines in the

setting of steroid-resistant cellular rejection that needs an additional immunosuppressant such as ATG. This practice is supported by the previously identified risk from receiving this lymphocyte-depleting agent in CMV-seropositive KT recipients [3]. Reusing et al demonstrated some benefit of anti-CMV prophylaxis in CMV-seropositive KT recipients who received ATG in a retrospective study [14]. More recently, Chiasakul and colleagues implemented targeted prophylaxis in those receiving a standard dose of ATG among high-risk patients such as those who underwent ABO incompatible KT with a favorable outcome [4]. Chitasombat et al specifically conducted a cost-effectiveness analysis, revealing that few KT recipients who received ATG were prescribed oral valganciclovir as outpatients. Therefore, they developed CMV infection more frequently compared with those receiving oral valganciclovir, ultimately leading to a longer duration of hospitalization and direct and indirect costs of treatment for CMV infection compared with those without CMV reactivation [15]. These data likely represent a burden of infectious complications among ATG-treated KT recipients, especially from CMV. More studies are required to better define the benefits of anti-CMV prophylaxis in these patient groups. In such individuals, anti-CMV prophylaxis is likely warranted, especially in those receiving immunosuppression augmented with ATG, and could be postulated for high-dose glucocorticoids.

The practice setting in Thailand is likely to have an impact on decision-making in terms of prevention strategies. Although substantial portions of our respondents worked in a public hospital setting where patients rely on the national and social security budget, we found that only a small portion of physicians who reported using CMV-specific T-cell immunity to design an intervention for their patients. This intervention has been encouraged in a recent guideline, because each patient is considered to have a different state of immunity against CMV, depending on their level of risk and immunosuppression [6, 16]. Recent data supported measurement of patients' nonspecific and CMV-specific immunity to better stratify prevention strategies for each KT recipient [17].

The most common barriers for establishing CMV prevention strategies in Thailand were lack of access to oral valganciclovir and quantitative CMV DNA testing due to high drug and laboratory assay costs, respectively. Based on the 2019 conversion rate of 32.5 THB to \$1 US, the cost of valganciclovir prophylaxis per 1 patient with normal glomerular filtration rate (900 mg/day) for 100 days was US \$7900, and the cost of weekly quantitative CMV DNA testing per 1 patient for 3 months was US \$936. Apart from the above mentioned, the impracticability of weekly measurement of plasma CMV DNA load was also an issue. Furthermore, a few participants reported an unacceptable side effect of bone marrow suppression from (val)ganciclovir.

Our study has several limitations. First, we saw a relatively low response rate of respondents in the NP group. Second,

only 1 ID and 1 NP were selected from each transplant center and these might not represent who the practice employed its entirety in that center. Lastly, other physicians who could be categorized outside of the ID and NP groups may be inadvertently excluded, even though they were potentially caring for KT recipients in some centers. Nonetheless, we have provided an overall picture of real-world CMV prevention awareness and practice in Thailand where resources are limited. This information will be helpful in highlighting the barriers faced, which must be addressed in a standardized guideline and direct efforts to implement a consistent practice for CMV prevention in Thai KT recipients.

In summary, although most physicians agreed that CMV prevention was necessary for Thai KT recipients, a nationwide survey revealed a lack of uniformity in prevention strategies for CMV infection after KT. A preemptive approach is the most common intervention used, though prophylaxis is preferred in patients receiving intense immunosuppression. The financial implication of specific drugs and laboratory tests is the main barrier for CMV prevention in Thailand. A practical guideline for CMV prevention in KT recipients would be valuable in attempting to resolve these concerns.

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