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# Cytomegalovirus in Solid Organ Transplant Recipients

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## Introduction and Epidemiology

CMV infection is a major cause of morbidity in patients receiving solid organ transplants. CMV is widely distributed in the general population with seroprevalence ranging from 30 to 97% (1–3). After primary infection, CMV establishes life-long latency. Without some form of prevention, CMV infection primarily occurs in the first 3 months following transplant. Onset may be delayed in patients receiving CMV prophylaxis.

The following definitions are commonly used in the transplant literature and are consistent with the AST recommendations for use in clinical trials (4):

(1) CMV infection: evidence of CMV replication regardless of symptoms (differs from latent CMV).
(2) CMV disease: evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as either a viral syndrome with fever and/or malaise, leukopenia, thrombocytopenia or as tissue invasive disease (e.g. pneumonitis, hepatitis, retinitis, gastrointestinal disease).

In addition, several features unique to pediatric transplantation are discussed separately in this document.

CMV has a predilection to invade the allograft, likely in part due to an aberrant immune response within the allograft (1). To directly attributable morbidity, CMV likely also has an immunomodulatory effect, and active CMV infection has been found to be an independent risk factor for the development of other infectious complications, such as bacteremia, invasive fungal disease and EBV-related PTLD (5,6). CMV has also been implicated as a cause of acute and chronic allograft injury. There is evidence that CMV may play a crucial role in chronic graft vasculopathy resulting in lesions, such as chronic allograft nephropathy, bronchiolitis obliterans (lung transplant) and accelerated coronary artery disease (heart transplant) (5,6).

## Risk Factors

The risk of CMV disease is highest in donor-positive, recipient-seronegative (D+R–) solid organ transplant patients who lack cellular and humoral immunity to CMV. Other risk factors for disease include the recipient's overall state of immunosuppression determined by the immunosuppressive protocol (e.g. type of drug, dose, timing, duration) and various host factors (e.g. age, comorbidity, neutropenia). Antilymphocyte antibodies (ALA) (such as thymoglobulin) as either induction or antirejection therapy are associated with high rates of CMV disease (1–3). The risk is maximal when ALA therapy is used for the treatment of organ rejection, with CMV disease being diagnosed three to four times more frequently than in patients not receiving ALA therapy (2). The risk of CMV also varies with the type of transplant. Lung, small intestinal and pancreas transplant recipients have the highest risk for CMV while liver and kidney recipients are at lower risk for CMV disease. This may be due to the degree of immunosuppression, and/or the viral load present in the transplanted allograft. Co-infection with related viruses such as HHV-6 and 7 may also be an important risk factor for CMV disease (1). The lowest risk of CMV disease occurs in the D–/R– setting, provided these patients are given CMV negative blood or leukodepleted blood products (1).

## Recommendations

(1) Pretransplant CMV IgG screening of donors and recipients should be performed to allow for risk stratification (II-1).
(2) CMV D–/R– transplant recipients should receive CMV negative blood or leukodepleted blood during and post-transplant (II-1).

## Laboratory Diagnosis

The diagnosis of CMV infection and disease has evolved considerably. Historically, the diagnosis of CMV disease has been made by histopathology. This approach is limited, however, by the fact that an invasive procedure is

required to obtain samples. Serologic assays appear to have limited clinical utility posttransplant, and should not be used to diagnose acute disease in SOT patients (7). For years, culture-based methods (tissue culture and shell-vial centrifugation culture) were used for CMV diagnosis. Tissue culture can take weeks, however, and the shell-vial centrifugation assay is insensitive by comparison with molecular assays (8). Tissue culture methods may still useful in growing CMV isolates in the laboratory for phenotypic antiviral resistance testing, although the latter technique has been replaced predominantly by genotypic resistance testing.

The pp65 antigenemia assay is a semi-quantitative fluorescent assay based on detection of infected cells in peripheral blood. This assay has far higher sensitivity and specificity than culture-based methods (8), and is comparable in sensitivity to CMV PCR (see further) (9). Though not fully quantitative, it can provide an estimate of the magnitude of viral load from the number of infected cells.

Molecular diagnostic tests may detect DNA or RNA and can be qualitative and quantitative. The majority of these tests are quite sensitive for the detection of CMV. Measurement of quantitative CMV-DNA levels has become popular at many centres. Commonly used assays include plasma or whole blood based PCR testing which is either commercially available or developed in-house. Whole blood assays will often have higher viral loads than those using plasma. Generally, the highest viral loads are associated with tissue-invasive disease, while the lowest are seen with asymptomatic CMV infection, and intermediate-range viral loads seen in patients with CMV syndrome (10); there is wide overlap, however, between these categories. In addition to the absolute value of viral load, the rate of rise is also an important factor (11). Occasionally patients with tissue invasive disease (especially gastrointestinal or retinal disease) will have undetectable blood viral loads. Both the pp65 antigenemia assay and quantitative CMV viral load testing can be utilized in preemptive protocols, for diagnosis of CMV disease, and to guide management of CMV disease (8–12). A lack of standardization between different centers is a major problem with all assays. A recent multicenter comparison of viral load assays demonstrated up to a 3-$\log_{10}$ variation among different assays. Standardization may be achieved in the future with quantitative viral load assays (13).

## Recommendations

(1) Culture based assays of blood and urine are of limited utility for prediction, diagnosis and management of CMV disease (II-2).
(2) Either the pp65 Antigenemia assay or a quantitative viral load assay should be used for most areas of management. Lack of standardization across different laboratories is a problem for both tests and centres need to validate their own threshold values (II-2).

**Table 1:** Prophylaxis versus pre-emptive therapy

| | Prophylaxis | Pre-emptive therapy |
|---|---|---|
| Efficacy | Yes: large randomized trials | Yes: smaller trials; fewer D+/R– |
| Ease | Relatively easy to coordinate | More difficult to coordinate; Test thresholds not standardized |
| Late onset disease | A potential problem | Much less commonly seen |
| Cost | Higher drug costs | Higher laboratory costs |
| Toxicity | Potential for greater drug toxicity (myelosuppression) | Potential for less drug toxicity with shorter courses of antivirals |
| Indirect effects (graft loss, mortality and opportunistic infections) | Consistent and positive impact based on meta-analyses and limited comparative trials | Very limited data that preemptive therapy affects indirect effects |

## Prevention: Prophylaxis and Preemptive Therapy

Approaches in the prevention of CMV in solid organ transplantation, and the results obtained, vary widely among different transplant programs. Reasons for this include insufficient large trials (especially comparing prophylaxis vs. preemptive therapy), different end-point definitions, multiple nonstandardized testing methodologies and differing patient populations.

Two strategies are commonly used for CMV prevention: (1) universal prophylaxis and (2) preemptive therapy. Universal prophylaxis involves giving antiviral therapy to all 'at-risk' patients (or a specified subset) beginning in the early posttransplant period for a defined duration (e.g. 3–6 months). In preemptive therapy, patients are monitored at regular intervals (often weekly) for early evidence of CMV replication by use of a laboratory assay. Patients with early replication are then treated with antiviral therapy to prevent symptomatic disease. Each approach has advantages and disadvantages that must be considered in the context of the patient and the allograft (14,15) (Table 1). Preemptive therapy may decrease drug costs and toxicity, but requires excellent logistic coordination, in order to obtain, receive, and act on results in a timely fashion, which can be difficult if patients live quite some distance from the transplant center. In addition, due to a lack of standardization of diagnostic testing, optimal threshold values for initiation of preemptive therapy have not been defined. Prophylaxis

**Table 2:** Currently available drugs for cmv prophylaxis

| Drug | Usual adult Prophylaxis dose | Comments on use and major toxicity |
|---|---|---|
| Valganciclovir | 900 mg once daily | Ease of administration; leukopenia |
| Oral Ganciclovir | 1 g three times daily | Low oral bioavailability; high pill burden |
| IV Ganciclovir | 5 mg/kg once daily | Intravenous access; leukopenia |
| Valacyclovir | 2 g four times daily | High pill burden; neurologic effects |

might have the theoretical advantage of preventing reactivation of other viruses such as HHV-6 and may be more likely to prevent indirect effects of CMV. Metanalyses have demonstrated that antiviral prophylaxis is associated with decreased rates of graft loss, improvement in survival and decreased incidence of opportunistic infections (16,17). Late-onset CMV disease is a potential problem with prophylaxis (see further). CMV resistance has been observed with both strategies (18,19). There are very few comparative randomized trials comparing preemptive therapy versus prophylaxis. Khoury et al. (20) randomized 98 kidney transplant recipients (D+/R– n = 29) to preemptive therapy (valganciclovir) versus prophylaxis (valganciclovir 100 days). Both strategies were equally effective in preventing CMV disease. Kliem et al. (21) randomized 148 renal transplant patients to preemptive therapy (I.V. ganciclovir) versus prophylaxis (3-months oral ganciclovir). Long-term graft survival at 4-years posttransplant was significantly improved in the prophylaxis group. In another study prophylactic valacyclovir was equivalent to preemptive valganciclovir in kidney transplant recipients (n = 70) for the prevention of CMV disease but the prophylactic regimen had a significant lower rate of biopsy proven rejection (15% vs. 36%, p = 0.034) (22).

## A. Universal Prophylaxis

Drugs that have been evaluated for universal prophylaxis include ganciclovir, valganciclovir, acyclovir, valacyclovir and immune globulin preparations (Table 2). Ganciclovir is available in both oral and intravenous formulations. There have been a number of randomized trials with varying agents that have been previously reviewed (1). Several large multicenter randomized trials of prophylaxis with agents including oral ganciclovir, valganciclovir and valacyclovir have also been performed (23–25). Valganciclovir is a valine ester prodrug of ganciclovir with improved bioavailability (50–60%) compared with oral ganciclovir (6–9%). In a trial of 372 D+/R– SOT recipients randomized to 3 months of prophylaxis with oral ganciclovir versus oral valganciclovir (PV16000), the rate of CMV disease at 6 and 12 months was comparable in the 2 arms (17.2% valganciclovir vs. 18.4% ganciclovir at 12 months) (25). In a trial comparing 200 versus 100 days of valganciclovir prophylaxis in 318 D+/R– kidney transplant recipients (Impact study), the incidence of confirmed CMV disease was 16.1% versus 36.8%, respectively (26). Less data are available in lung transplant recipients, but studies suggest that rates of viremia and disease are high with short courses of prophylaxis and lower with longer courses of prophylaxis (6 months or more) (27,28). Benefit for indirect effects has been more difficult to demonstrate in individual studies. Valacyclovir (8 g/day, adjusted for renal function) administered for 90 days reduced the incidence of biopsy-proven acute rejection in CMV-seronegative patients (24). Acyclovir has less activity and is not recommended specifically for CMV prophylaxis.

The efficacy of prophylaxis with either CMV immune globulin (CMVIG) or intravenous immune globulin (IVIG) in solid organ transplant recipients has been investigated in relatively few trials (29,30), and the majority of those conducted have been randomized, but nonblinded. Further research is needed to delineate the benefit of adding immune globulin to current CMV prophylaxis regimens.

### *Late onset CMV disease*

The major problem with CMV prophylaxis continues to be late-onset CMV disease. This can be defined as disease occurring sometime after discontinuation of antiviral prophylaxis. For 3-month prophylaxis regimens, this typically occurs between 3 and 6 months posttransplant or sometimes later (25). Disease presenting late may be missed due to difficulties in diagnosis, especially for patients living at geographical locations removed from their primary transplant program. Late onset disease contributes to morbidity and has been shown to be associated with higher overall mortality (31). The incidence of late-onset disease with a standard 3-month course of prophylaxis is estimated to be approximately 17–37% among D+/R– recipients, with higher rates when current definitions of CMV disease are used (25,32).

Potential options for dealing with late-onset CMV disease are as follows:

(1) Careful clinical follow-up with treatment of disease as soon as symptoms occur.
(2) Virologic monitoring after completion of prophylaxis. Check antigenemia or viral load periodically for 8–12 weeks after completion of prophylaxis. However, studies evaluating the utility of monitoring after prophylaxis have demonstrated poor sensitivity and specificity for prediction of CMV disease (33). Weekly monitoring would likely be required to be successful.
(3) Prolong prophylaxis from 3 to 6 months in D+/R–. The Impact trial demonstrated a significant reduction in CMV disease using 200 days of prophylaxis versus 100 days in D+/R– kidney transplant recipients (32). Further research is needed to extrapolate this to R+ patients.

## Specific Recommendations for CMV Prophylaxis

All doses should be adjusted based on renal function. Specific anti-CMV prophylaxis in D–/R– patients is generally not needed provided CMV negative blood or leukodepleted blood products are used.

### Kidney and Liver Transplant Recipients

(1) In D+/R– kidneys and livers, valganciclovir 900 mg/day, oral ganciclovir (3 g/day), or intravenous ganciclovir (5 mg (kg/day)) prophylaxis are effective for prevention of CMV disease (I). In kidney transplant recipients, valacyclovir 8 g/day is an alternative (I). The FDA has a caution against the use of valganciclovir in liver transplant patients but many experts still recommend its use in this setting and it is used in 60% of U.S. transplant centers (34)
(2) Start prophylaxis within 10 days posttransplant and continue until ~3 to 6 months posttransplant (I).
(3) In R+ kidney or livers, oral ganciclovir, valganciclovir, intravenous ganciclovir, or valacyclovir (kidneys) for 3 months decreases the rate of CMV disease (same doses).

### Heart Transplant Recipients

(1) For D+/R– heart transplant recipients valganciclovir (900 mg/day), oral ganciclovir (3 g/day) or intravenous ganciclovir (5 mg/(kg day)) for 3–6 months can be used for prophylaxis (I).
(2) Some centers add CMVIG for prophylaxis (II-2)
(3) In R+ recipients, oral valganciclovir (II-2), intravenous ganciclovir (II-1), or oral ganciclovir for 3 months are effective (same doses).

### Pancreas and Kidney/Pancreas Recipients

(1) There is limited RCT data in pancreas transplant recipients, but generally they are thought to be at high risk for CMV disease. Options include for D+/R– or R+: valganciclovir (900 mg/day) (II-2), intravenous ganciclovir (5 mg/kg/day) or oral ganciclovir (3 g/day) for 3–6 months (II-2).

### Lung and Heart-lung Transplant Recipients

There is limited randomized clinical trial data for lung transplant recipients; in general, these patients are at the highest risk for CMV disease.

(1) D+/R– lung transplant recipients may be given prophylaxis with intravenous ganciclovir (5 mg/kg/day) or oral valganciclovir (900 mg/day) for 6 months (II-2). Given the high rate of late onset CMV disease in this subgroup some centres prolong the duration of prophylaxis beyond 6 months (II-2).
(2) For D+/R+, D-/R+ lung transplant recipients, prophylaxis with oral valganciclovir, intravenous ganciclovir, or oral ganciclovir for 3–6 months may be used (II-2) (same doses as aforementioned).
(3) CMVIG is used by some centres in conjunction to antiviral therapy in high risk lung transplant recipients (II-2).

**Table 3:** Guidelines for cmv prevention in sot recpients

| Organ/group | Recommendation/Options (see text for dose, evidence rating and special pediatric issues) |
|---|---|
| Kidney, liver, pancreas, heart | • Prophylaxis: valganciclovir, oral ganciclovir, or intravenous ganciclovir (or valacyclovir in kidney) for 3 to 6 months. Some centers add CMV immune globulin for heart transplant. |
| D+/R– | • Preemptive therapy an option (see Figure 1). Many authorities prefer to use prophylaxis and reserve preemptive therapy for lower-risk populations (see text). |
| Kidney, liver, pancreas, heart | • Valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir (kidney) for 3 months. Some centers add CMV immune globulin for heart transplant *OR* |
| R+ | • Pre-emptive therapy an option (see Figure 1). |
| Lung, heart-lung | • For D+/R– patients valganciclovir or intravenous ganciclovir for 6 months. Some centres will prolong prophylaxis beyond 6 months. |
| D+/R–, R+ | • For R+ patients, valganciclovir, oral ganciclovir or intravenous ganciclovir for 3–6 months.<br>• Some centres will add CMV immune globulin especially for D+/R–. |

The above guidelines do not represent an exclusive course of action. Several factors may influence the precise nature and duration of prophylaxis or preemptive therapy.

### Intestinal Transplant Recipients

There are more limited data in this patient population. For D+/R– and for R+, valganciclovir (900 mg/day), intravenous ganciclovir (5 mg/(kg day)) or oral ganciclovir (3 g/day) for 3–6 months are recommended (III). CMVIG is used by some centers in conjunction to antiviral therapy (III).

## B. Preemptive Therapy

Preemptive therapy involves monitoring of patients for early evidence of CMV replication with early treatment to prevent symptomatic disease (Table 3) (1–3). Preemptive therapy has the potential advantage of targeting therapy

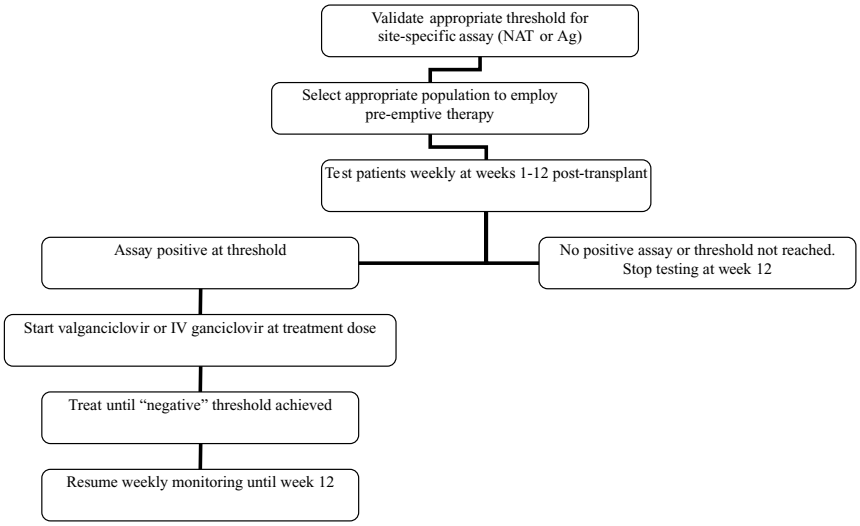


**Figure 1: Suggested algorithm for preemptive therapy.**

to the highest risk patients and thereby decreasing drug costs and toxicity. Several aspects make up a preemptive strategy including (see Figure 1): (1) selection of the appropriate population for preemptive therapy, (2) determining the optimal laboratory test and duration of monitoring and (3) choosing the type, dose and duration of an antiviral agent. Based on current data, a preemptive algorithm is shown in Figure 1. Either the pp65 antigenemia assay or CMV viral load testing should be utilized. Site specific and assay specific threshold values for initiation of preemptive therapy should be locally validated prior to institution of a preemptive protocol (10).

Once viremia is detected, treatment with either valganciclovir or intravenous ganciclovir should be initiated. In a randomized trial comparing the two agents for treatment of mild to moderate CMV disease, both agents had equal efficacy (12). Because preemptive therapy should treat low-level asymptomatic viremia, oral valganciclovir is likely preferable to intravenous ganciclovir for logistic issues.

## Preemptive Therapy Recommendations

(1) Preemptive therapy is a suitable option for patients at risk for CMV disease (I). Considerable controversy exists about the best population in which to use a preemptive strategy. Many authorities prefer prophylaxis for the higher risk D+/R– group while recognizing the potential utility of preemptive therapy in the R+ group.
(2) The best laboratory test for monitoring is either a CMV viral load test or a pp65 antigenemia assay (II-2). The optimal monitoring strategy is approximately once weekly testing for 12 weeks posttransplant (II-2).
(3) The optimal drugs for preemptive therapy are oral valganciclovir (900 mg two times a day) or intravenous ganciclovir (5 mg/kg two times a day) (I). Therapy should be continued until viremia is undetectable (II-2).
(4) Further studies are required to determine comparative efficacy of preemptive therapy versus prophylaxis, especially regarding the indirect sequelae of CMV.

## C. CMV Prevention During ALA Therapy and/or Treatment of Rejection

The use of ALA therapy is a major risk factor for CMV disease especially when used for the treatment of rejection. Its effect on antiviral efficacy has been explored in three trials in solid organ transplant recipients (35–37). In two of the trials, in which intravenous ganciclovir was compared with no therapy in kidney transplant recipients receiving ALA (35,36), there was evidence of a protective effect of ganciclovir.

## Recommendations

(1) Prophylaxis with antiviral therapy should be given in patients receiving ALA therapy either as induction or for the treatment of rejection (I). The optimal duration of antiviral therapy is not known. Options include valganciclovir (III), oral ganciclovir (III) or intravenous ganciclovir (I) for approximately 1–3 months.
(2) Alternatively a preemptive therapy protocol can be instituted in these patients (III). See Figure 1.
(3) In patients treated for acute rejection with high dose steroids, resumption of prophylaxis or a preemptive strategy may be considered as earlier (III).

## Treatment of Established CMV Disease

Intravenous ganciclovir has been used successfully in over 30 uncontrolled, nonrandomized, therapeutic trials to treat solid organ transplant recipients with CMV disease (1,2) and has been considered the mainstay for therapy. The

typical dose of intravenous ganciclovir for treatment is 5 mg/kg twice per day. The duration of therapy in trials varied from 2 to 4 weeks. Valganciclovir at a dose of 900 mg twice daily achieves levels similar to intravenous ganciclovir treatment. In a randomized controlled trial comparing 3 weeks of oral valganciclovir to IV ganciclovir for the treatment of CMV disease in 321 organ transplant patients (the vast majority were kidney transplant recipients) with mild to moderate CMV disease, both drugs had similar efficacy for the eradication of viremia at 21 days posttreatment (12). In the per-protocol population, a significant number of patients had persistent viremia at day 21 suggesting longer courses of therapy should be administered in many patients. While oral ganciclovir has been shown to *prevent* CMV disease, its utility in the *treatment* of CMV disease is not recommended.

Overall, molecular diagnostic tests can be used to tailor the duration of antiviral therapy in each patient based on clearance of CMV viral load or antigenemia. This risk of relapse is lower in patients who have no detectable CMV viral load at the end of therapy than for those with detectable CMV viral load (38,39). Therefore, patients with evidence of CMV viremia should be maintained on therapy until viremia (measured either by antigenemia or nucleic acid testing) has dropped below the negative threshold value for a given test. With ultra-sensitive assays, this negative threshold value has not been well defined.

## Summary Recommendations for Treatment of Established CMV Disease

(1) In any solid transplant recipient, CMV disease should be treated with either intravenous ganciclovir (5 mg/kg two times a day) (I) or oral valganciclovir (900 mg two times a day) (I) until the following criteria are met:
   a. Clinical resolution of symptoms AND;
   b. Virologic clearance below a threshold negative value (test specific; see text); monitor patients with viral load or pp65 antigenemia once a week AND
   c. Minimum 2 weeks of treatment;

(2) Intravenous ganciclovir is preferable to oral valganciclovir in patients with severe or life-threatening disease, or in patients who may have a problem with gastrointestinal absorption of oral drug (e.g. significant diarrhea).

(3) Acyclovir and oral ganciclovir are not effective in treating CMV disease in transplant recipients (II-2). Oral ganciclovir treatment in the presence of CMV replication may lead to emergence of ganciclovir resistant CMV strains (II-2).

(4) It is unclear whether addition of IVIG or CMVIG to existing treatment regimens has a benefit for solid organ transplant recipients (II-2) but may be considered for patients with CMV pneumonitis and possibly other severe forms of disease.

(5) After completion of treatment, a 1–3 month course of secondary prophylaxis may be considered depending on the clinical situation (III). Alternatively close clinical and/or virologic follow-up after discontinuation of treatment is an option (III).

## Ganciclovir Resistant CMV

Ganciclovir undergoes initial phosphorylation by a viral kinase encoded by the gene UL97. After subsequent triphosphorylation by cellular enzymes the active drug inhibits CMV DNA polymerase encoded by the gene UL54. Mutations in UL97 and less commonly in UL54 can confer ganciclovir resistance. UL97 mutants often have only low-level resistance to ganciclovir depending on the site of mutation and hence therapeutic response may still be observed in some cases. Combined mutations (UL97 and UL54) often have high-level resistance to ganciclovir. Foscarnet is a potent anti-CMV agent, and has activity against most ganciclovir resistant strains of CMV. There are far fewer studies of foscarnet in solid organ transplant recipients than there are of ganciclovir; however, the majority of transplant patients treated with foscarnet, either alone or in combination with ganciclovir, did improve (40–42). Additionally, multiple isolated cases of CMV disease caused by ganciclovir resistant CMV strains have been successfully treated with IV foscarnet. The major problem in transplant patients is significant nephrotoxicity. The full extent of side effects of foscarnet in solid organ transplantation remains to be determined. Cidofovir is used for the treatment of CMV infection in individuals with HIV/AIDS and although evaluated in transplant settings, no controlled studies have yet been formally published. Cidofovir has significant nephrotoxicity as well. CMV isolates with UL97 mutations may remain sensitive to foscarnet and cidofovir. UL54 mutations may result in resistance to these drugs depending on the site of the mutation.

The incidence of ganciclovir resistant CMV remains generally low in most settings after solid organ transplant. In the PV16000 study the overall rate of resistance was 1.9% in those who received oral ganciclovir versus 0% among those receiving valganciclovir (43). However in some subpopulations (especially lung transplantation) higher rates of resistance have been reported (44). Risk factors for resistance include prolonged low-dose oral prophylaxis (e.g. with ganciclovir or valganciclovir), D+/R– serostatus, increased intensity of immunosuppression and lung transplantation (18). Resistance should be suspected if (1) the patient has received prolonged antiviral prophylaxis, (2) the viral load fails to decrease or increases despite two weeks of adequate dose antiviral therapy and (3) patients have other risk factors for resistance as outlined above. Genetic resistance testing may be very helpful in managing resistant CMV. An algorithm for treatment of ganciclovir resistance CMV disease is presented in Figure 2.

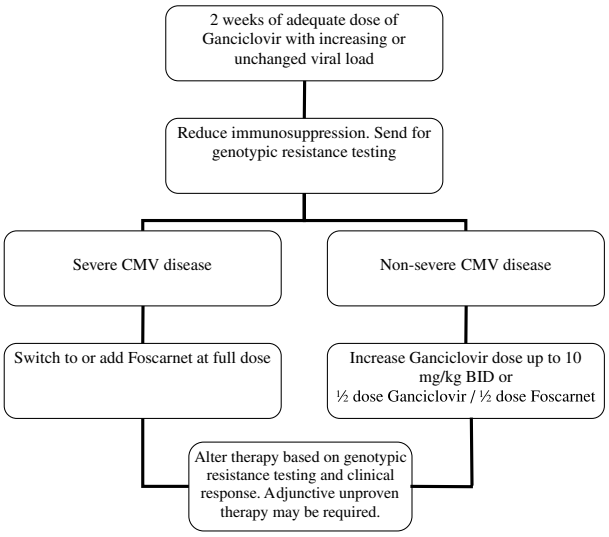


**Figure 2: Algorithm for treatment of ganciclovir resistance.**

## Recommendations for Ganciclovir Resistant CMV

(1) Patients who develop CMV disease after prolonged courses of ganciclovir or valganciclovir prophylaxis and those failing to respond to standard ganciclovir treatment should be suspected of having ganciclovir resistant virus. Genotypic testing for resistance should be performed (III).
(2) Immunosuppression should be reduced or discontinued (III).
(3) Therapeutic options include increasing the dose of intravenous ganciclovir (up to 10 mg/kg two times a day) or foscarnet (alone or in combination with low dose ganciclovir) (see Figure 2) (II-2).
(4) For refractory cases unproven or untested therapeutic options may be considered and include cidofovir, compassionate release maribavir, leflunomide and artesunate (III).
(5) The role of CMVIG in this setting is unknown but may be considered (III).

## Pediatric Issues

In general there are less data available for pediatric transplant populations with regards to CMV prevention and treatment. In addition, other issues such as prevention of EBV-related PTLD, may be of more importance in this population and affect the choice of CMV prevention strategies. Overall, proportionately more pediatric patients are at risk of developing primary CMV infection and hence severe disease by virtue of being CMV-seronegative prior to transplantation. While many donors for pediatric patients will also be seronegative, the use of living-related or split decreased donor organs (as in liver transplantation) results in a marked frequency of high risk (D+/R–) pediatric organ recipients. The following recommendations specific to pediatric patients can be made:

### *Pretransplant screening (pediatrics)*

(1) Pediatric transplant recipients <18 months of age may have passively acquired maternal antibody. Urine culture should be performed. If urine culture positive assume recipient seropositive. If negative, assign recipient serostatus based on the highest risk level for the purposes of CMV prevention (III). For donors <18 months age, if seropositive assume donor is seropositive (II-2).

### *Prevention and treatment (pediatrics)*

The principles and recommendations for the use of prophylaxis and pre-emptive therapy in adult recipients are generally applicable to pediatric organ transplant recipients with the following qualifying statements.

(1) Data are limited regarding the efficacy of pre-emptive therapy in pediatric organ transplant recipients.
(2) Data are lacking on the appropriate dose and efficacy of oral ganciclovir and oral valganciclovir in children. Treatment and prevention strategies continue to be based primarily on intravenous ganciclovir especially in younger children.
(3) The duration of intravenous ganciclovir is influenced by the risk of catheter-associated bloodstream infections in some settings. The duration of prophylaxis is also influenced by other factors that vary across centres. These factors include the types of organ transplanted, the institution's experience with CMV disease in their patient population, immunosuppressive practices and the institution's consensus-driven EBV prophylaxis regimen (45) (I).
(4) In this aforementioned context, there is no single standard of care as this relates to the precise duration of prophylaxis. The duration of intravenous ganciclovir prophylaxis in major centres varies from a minimum of 14 days to 3 months (II-2).
(5) Treatment of CMV disease in particular should be with intravenous ganciclovir due to a lack of efficacy data of oral therapy in the pediatric population. CMVIG is considered by some experts in combination with ganciclovir for the treatment of CMV disease in young infants and for treatment of more severe forms of CMV disease (III).

## Future Research Directions

There are a number of areas that are being actively explored in basic, translational and clinical research fields. A number of in-house and some commercially available assays for the assessment of T-cell immunity to CMV are

being evaluated for their ability to predict the development of CMV disease. It is hoped that these assays will allow better risk-stratification of patients and allow more targeted prevention strategies. Preventive and therapeutic strategies being evaluated include CMV vaccines and novel drugs. The drug closest to development is Maribavir, an inhibitor of CMV UL97. In a phase 2 study in hematopoietic stem cell transplant (HSCT) recipients, maribavir prophylaxis was superior to placebo for the prevention of CMV viremia (46). However, a phase 3 studies in HSCT recipients failed to meet its primary endpoint and the future of this drug is uncertain. Finally, further studies of CMV prevention and treatment are required for pediatric transplant recipients.

## Disclosure

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