Summary of the British Transplantation Society Guidelines for the Prevention and Management of CMV Disease After Solid Organ Transplantation

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The third edition of the British Transplantation Society Guidelines for the Prevention and Management of CMV Disease after Solid Organ Transplantation was published in March 2011 (1). Developed by a working group of the British Transplantation Society, the last date of formal literature review was October 2010, although additional references were included during the review process. The guideline has been extensively revised since the previous edition in 2005 and has used the GRADE system to rate the strength of evidence and the strength of recommendations (2). This approach is consistent with that adopted by Kidney Disease Improving Global Outcomes in its recent guidance relating to renal transplantation and also with guidelines from the European Best Practice Committee and the UK Renal Association (3–5). Complementing previous guidance published by the American Society of Transplantation/American Society of Transplant Surgeons, Kidney Disease Improving Global Outcomes and the Transplantation Society (6), they thus represent the most up-to-date synthesis of the evidence in this rapidly evolving field.

Diagnosis and Prevention of Cytomegalovirus Disease

After primary infection, cytomegalovirus (CMV) establishes life-long latency. One challenge in the transplant recipient is therefore the differentiation of patients with active CMV infection who are at risk of tissue invasive CMV disease from those who have subclinical infection. In this review, we use the term latent to define a state of virus infection which for which the full replication cycle of the virus is not occurring, whereas active infection is defined as a state where there is evidence of virus undergoing a complete replication cycle and producing new infectious virions. Active infection can be further characterized into asymptomatic infection (no obvious signs of pathologic symptoms), viral syndrome (fever, leucopenia, myalgia, or arthralgia), and CMV disease (fever >38°C for 2 days of unexplained origin and one of leukopenia, myalgia, or arthralgia), and CMV disease (his-
topathological evidence of CMV, CMV retinitis diagnosed by an ophthalmologist, or CMV in the CSF indicative of CNS disease).

The frequency of CMV disease varies markedly depending on the definition used and the intensity of immunosuppression. Approximately 8% of renal, 29% of liver, 25% of heart, and 39% of lung transplant recipients experience symptomatic infection (7).

CMV load, used as a surrogate marker of CMV replication, has been shown in many studies to be a dominant risk factor for CMV disease. Increased experience and the availability of commercial assays have now allowed polymerase chain reaction (PCR) diagnosis and monitoring to be offered on a routine basis (8, 9), with real-time PCR offering highly reproducible and rapid data on viral load (10). The objective of modern management is to avoid patients reaching a clinical endpoint of CMV syndrome or tissue invasive disease.

Two approaches are in common use to minimize the impact of CMV infection or reactivation in solid organ transplantation: universal or targeted anti-CMV prophylaxis; and pre-emptive anti-CMV therapy. In some units, both approaches are used, depending on the donor/recipient CMV status, organs transplanted, and intensity of immunosuppression. The following sections summarize the evidence for the most commonly adopted strategies.

**Universal Anti-CMV Prophylaxis**

In this approach, subgroups of “at-risk” patients are offered prophylactic antiviral therapy for a defined period posttransplantation, at doses designed to prevent disease. Therapy is usually offered to donor positive/recipient negative for previous CMV infection (D+/R−) combinations to prevent primary infection, less commonly to D+R+ combinations to minimize reactivation of latent virus and infection with new genotypes, and occasionally to donor negative/recipient positive for previous CMV infection (D−/R+) combinations to prevent reactivation.

A number of antiviral agents have been shown to be effective. Agents currently in use include ganciclovir (oral and intravenous preparations), valaciclovir, and valganciclovir. Some centers use CMV immune globulin, especially for D+/R− heart and heart-lung transplantation. A summary of current organ-specific recommendations is given in Table 1.

The major change in clinical practice since the second edition of the guidelines is that most units involved in solid organ transplantation use valganciclovir rather than intravenous ganciclovir as first-line CMV prophylaxis. Recent evidence regarding the use of this agent will therefore be considered in some detail.

The key licensing data came from a randomized double-blind multicenter study that recruited 364 adult CMV-negative recipients of CMV-positive solid organ transplants randomized 2:1 to valganciclovir or oral ganciclovir prophylaxis (11, 12). Treatment started within 10 days of transplantation and continued until 100 days after surgery. The frequency of CMV disease in the first 6 months was 17.2% in the valganciclovir compared with 18.4% in the ganciclovir-treated group. After 6 months, CMV disease occurred in 5% of the valganciclovir and 3.2% of the ganciclovir-treated group. At the end of the 3-month prophylactic period, the incidence of ganciclovir-resistant CMV strains was low at 0% for the valganciclovir and 1.9% in patients who had received oral ganciclovir (13).

The evidence base for CMV prophylaxis is suboptimal and varies according to the organ transplanted. Most data show oral valganciclovir and intravenous ganciclovir to be broadly equivalent, but the absence of comparative trial data makes intravenous ganciclovir a preferred option in many transplant situations. A pragmatic approach balances the limited evidence base against clinical experience. Although the Federal Drug Authority has not licensed oral valganciclovir for CMV prophylaxis in liver transplantation, accumulating evidence and expert opinion means that most liver transplant units in the United States and United Kingdom now use such prophylaxis. Similarly, although the best available evidence supports the use of intravenous ganciclovir for prophylaxis in simultaneous kidney-pancreas and cardiac transplantation, many units use oral valganciclovir to avoid the costs and inconvenience of hospital admission or home intravenous antiviral therapy.

The length of posttransplant prophylaxis has been mainly studied in renal transplantation. The IMPACT study was a double-blind, randomized, controlled study that compared 326 D+/R− renal transplant recipients randomized 1:1 to 200 days prophylaxis with valganciclovir versus 100 days prophylaxis followed by 100 days treatment with placebo (14). The rate of biopsy-proven acute rejection was not significantly different, the rates of graft loss were low, and renal function was equal in the two groups. The rate of other opportunistic infections was significantly higher in the 100-day treatment arm, but this was almost entirely due to an increase in infections seen in the first 50 days. It is biologically implausible to ascribe this difference to drug therapy (or placebo) that was not due to start for another 50 days. The rate of CMV viremia at 12 months was 51% in the 100-day arm and 37% in the 200-day treatment arm (P<0.05). The primary efficacy parameter was the proportion of patients who developed “CMV syndrome” or tissue invasive CMV within the first 52 weeks. “CMV syndrome” was defined as CMV viremia with at least one of fever, malaise, leucopenia, thrombocytopenia, or hepatitis. This definition of CMV syndrome and that of tissue invasive disease was congruent with that recommended by American authorities (15). In contrast to most studies, however, the authors of this study chose to define CMV disease as a combination of tissue-invasive CMV or CMV syndrome defined earlier (14). Using this broadened definition of disease, “CMV disease” was seen at 1 year in 16% of the 200-day treatment group versus 37% of the 100-day treatment group (P<0.0001), of which 97.6% was “CMV syndrome.” Three patients experienced tissue invasive disease (all gastrointestinal), two in the 100-day treatment group and one in the 200-day treatment group (not significant).

When deciding whether doubling the length of prophylaxis with valganciclovir achieved a clinically useful risk-benefit ratio, one key assessment is how worthwhile it might be to approximately halve the rate of CMV disease, as defined by these authors. Of the CMV syndrome observed, which represented 97.6% of all CMV recorded, 45 of 59 cases in the 100-day group and 20 of 24 cases in the 200-day group were rated by the local investigator as of mild-to-moderate severity. The local clinicians decided to treat 57 of 59 of those with.
CMV syndrome in the 100-day group and all 24 patients with CMV syndrome in the 200-day group. This indicates that the local clinicians thought that the level of ill health justified treatment in these cases and implies that they believed it was better to treat at this stage rather than wait until the patients’ condition had potentially worsened.

The impact of this study on clinical practice has varied across transplant centers in the United Kingdom, with some moving to a universal policy of 200 days of CMV prophylaxis in the D+/R+ group, others continuing with a policy of 100 days of prophylaxis with a longer period for patients following treatment of rejection or at a perceived higher infective risk. This may reflect reluctance to extrapolate from a single study in which a nonstandard definition of disease was adopted, together with concerns regarding the cost of additional therapy.

A study supported by the drug manufacturer examined the cost-effectiveness of extended therapy in the United States and indicated that such treatment reduced the incidence of CMV disease (syndrome) at a cost of $15,000 per QALY (16). Such economic analyses are subject to many input variables and should be treated with caution, and the results may not be generalizable to other health care systems. However, the Scottish Medicines Consortium recently accepted that extending valganciclovir prophylaxis to 200 days was probably cost-effective in CMV D+/R− transplants (17).

TABLE 1. Summary of recommendations

For references and details regarding these recommendations, please see the full guidelines (1).

For prevention

Where both donor and recipient are seronegative for CMV, leuko-depleted blood and blood products should be used to minimize the risk of primary infection. In this situation, no prophylaxis or monitoring is required.

CMV seronegative recipients who receive a solid organ transplant from a seropositive donor should be offered prophylaxis against primary infection. The same should apply where the donor or recipient is seropositive if the patient is treated with T-cell depleting antibodies.

For renal transplant recipients, recommended management is one of the following:
- Oral valganciclovir for at least 100 d.
- Oral valganciclovir for 200 d.
- Serial measurements of viral load and treatment with oral valganciclovir or intravenous ganciclovir when levels predictive of disease are reached.

For liver transplant recipients, recommended management is one of the following:
- Oral valganciclovir for 100 d.
- Intravenous ganciclovir for 100 d.
- Serial measurements of viral load and treatment with oral valganciclovir or intravenous ganciclovir when levels predictive of disease are reached.

For kidney/pancreas transplant recipients, recommended management is one of the following:
- Oral valganciclovir for 100–200 d.
- Serial measurements of viral load and treatment with intravenous ganciclovir when levels predictive of disease are reached.

For lung transplant recipients, recommended management is as follows:
- Oral valganciclovir for 100–360 d.

For heart transplant recipients, recommended management is one of the following:
- Oral valganciclovir for 100 d.
- Intravenous ganciclovir followed by oral valganciclovir for 60 d.
- Serial measurements of viral load and treatment with intravenous ganciclovir when levels predictive of disease are reached.

When the donor and recipient are both seropositive and the patient is not treated with T-cell depleting antibody therapy:

For renal transplant recipients, no prophylaxis is recommended.

For liver transplant recipients, no prophylaxis is recommended.

For heart transplant recipients, no prophylaxis is recommended.

For lung transplant recipients, the recommended prophylactic strategy is as follows:
- Oral valganciclovir for 100 d.

In all of these D+/R+ patients, serial measurements of viral load and treatment with oral valganciclovir or intravenous ganciclovir can be deployed when levels predictive of disease are reached.

For treatment

Patients with CMV disease should receive oral valganciclovir or intravenous ganciclovir until resolution of symptoms and for a minimum of 14 d.

Foscarnet and cidofovir are second-line therapeutic options unless ganciclovir resistance has been demonstrated.

Intravenous immunoglobulin may be of value, but the evidence base is poor.

Consideration should be given to a reduction in immunosuppression.

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The recommended dose of valganciclovir is 900 mg once daily for patients with normal renal function, with reduction in dose at lower levels of GFR. A recent meta-analysis is pertinent (18). This described the comparative use of 900 mg vs. 450 mg of valganciclovir as prophylaxis against CMV in solid organ transplant recipients, with more than 1500 patients analyzed in each treatment arm. No difference was identified in the incidence of CMV using the lower dose of valganciclovir, but the 900 mg dose was associated with an increased risk of leukopenia (odds ratio 3.32; \( P<0.0002 \)) and—surprisingly—an increased risk of rejection (odds ratio 2.56; \( P<0.005 \)). These risks persisted after adjustment for the type of allograft, CMV control strategy, and immunosuppression. The interpretation of these data is not clear, but a linked editorial (19) recommends further study of the dose requirements for extended CMV prophylaxis, while noting the risk of an increased rate of antiviral resistance when using the lower drug dose.

The evidence base for prolonged CMV prophylaxis is more limited for lung than for renal transplantation. However, in a study published in 2010 involving 11 U.S. centers, 136 lung transplant recipients who had completed 3 months of valganciclovir prophylaxis were randomly assigned to treatment with valganciclovir or placebo for an additional 9 months (20). CMV infection defined as disease or positive viremia or bronchoalveolar lavage culture but not meeting the primary end point occurred in 32% of short-course vs. 4% of extended-course treatment \( (P<0.001) \), whereas total CMV infection occurred in 64% vs. 10%. There was no difference in other secondary endpoints which included acute rejection, opportunistic infection, ganciclovir resistance, and safety. In these guidelines, prolonged antiviral prophylaxis has been recommended in lung transplantation because of high infection rates and the observation that the lung seems to be particularly badly affected by CMV infection. More data would be welcome.

Pre-Emptive Anti-CMV Therapy

In this approach, which is largely confined to renal transplantation, patients undergo regular surveillance and are treated when judged to be at high risk of developing CMV disease. Treatment is usually with full-dose valganciclovir as the kinetics of decrease in viral load has been shown to be the same as for intravenous ganciclovir (21). A variety of markers for predicting future CMV disease have been described and results should be interpreted in terms of the rapid dynamics of CMV replication as the average doubling time is rapid (between 1 and 2 days) (22, 23). The absolute levels of viremia that are recommended as a threshold to start preemptive therapy will depend upon the assay used. For example, most real-time PCR assays (which are popular because of simplicity and high level of automation) report lower levels of viremia compared with the Hybrid Capture Assay. Ideally, units should establish the clinical significance of their local assay, although there is now a universal standard for CMV nucleic acid testing produced by NIBSC (United Kingdom), which should reduce interlaboratory variation and facilitate multicenter approaches to antiviral trials and patient management (24).

That preemptive therapy can be used to control CMV disease has been demonstrated in many studies and in several meta-analyses. For example, in a study of 52 asymptomatic renal transplant recipients, 23 (44%) had positive CMV PCR tests on at least one occasion. However, only 2 (8.6%) developed CMV disease. This study suggests that, in this population with this assay, a treatment strategy based on positive PCR alone would treat a significant number of patients who did not necessarily require it (25). The authors reported the important finding that none of the 29 patients who were continuously negative for CMV PCR developed CMV disease. Similar studies have demonstrated efficacy of preemptive therapy in renal (26), bone marrow (27), liver, and cardiac transplantation (28).

The duration of preemptive antiviral therapy is important. The optimum length of treatment has not been determined, although some authors have recommended a minimum period of 4 weeks. It is logical to be guided by serial measurements of the viral load, and others have recommended treatment continue for 1, 2, or 4 weeks after the patient has tested negative for viral replication (29). There is no trial evidence to inform the required frequency of viral load estimation, but expert opinion and the kinetics of viral replication suggest that such assessment should be performed at least weekly.

The authors of a review of prophylaxis strategies for CMV in solid organ transplantation commented on what has been termed “targeted prophylaxis” in these guidelines and pointed out that “conventional prophylactic therapy has a large body of supportive controlled clinical studies demonstrating efficacy and cost-effectiveness. The strategy has the advantage of preventing other herpes viruses. There is some information to suggest that prophylactic therapy may benefit by reducing rejection” (30). The authors contrast preemptive therapy, pointing out “it is limited by reliance on intensive surveillance with significant logistic difficulties and requiring good patient compliance. There is ambiguity about the best surveillance method and the purported benefits of preemptive therapy, such as decreased cost, fewer adverse medication effects and less anti-viral resistance have not been proven in head to head clinical studies.” In the counterpoint article published simultaneously, the problems of prophylaxis were discussed (31). These include preventing antigen presentation to the immune system so that patients are at risk of developing disease once the drug is stopped and the risk of drug resistance. More recent reviews have advocated targeted prophylaxis (32), the advantages of preemptive therapy (33), and the possibility of different approaches in each serological combination (34, 35).

One theoretical concern with a preemptive approach is that it would not be expected to protect from the indirect effects of CMV infection, including any influence on late graft and patient survival (36). A recent randomized controlled study in kidney transplant patients compared preemptive therapy with prophylaxis with oral ganciclovir (37). These data suggest that graft survival at 4 years posttransplantation was significantly worse in patients who had been managed preemptively. More data are needed in this area but the suggestion is that prophylaxis interrupts initial organ amplification of CMV, and hence minimizes effects on the graft, both in the early period posttransplantation and also potentially in the longer term.

Both prophylaxis and preemptive therapy are effective at controlling CMV disease. Colleagues should discuss the
practicalities with their local virologists and audit their agreed management strategy. The majority of UK units have adopted a targeted prophylaxis strategy.

**CMV Vaccination**

Recent studies have seen considerable progress towards the "holy grail" of an effective CMV vaccine. In 2009, a phase 2 trial reported the use of a vaccine containing recombinant CMV glycoprotein B subunit antigen combined with MF59 adjuvant for the prevention of CMV infection in seronegative women of childbearing age. The primary end point was the time to CMV infection in the women and the vaccine was found to be 50% effective (95% confidence interval, 7–73) (38).

This is a rapidly evolving field and recent results of a phase 2 study in solid organ transplant patients with the same gB-MF59 vaccine have indicated that the vaccine is highly immunogenic in CMV-seronegative individuals and can boost immunity in CMV-seropositive individuals. In addition, in those patients who proceeded to transplantation, there were encouraging indications that vaccinated patients required less antiviral therapy and that the incidence of infection was reduced in the high-risk D+R− group (39). These results are encouraging and should stimulate the evaluation of further vaccines in solid organ transplant recipients and phase 3 studies of the gB-MF59 vaccine.

**Treatment of CMV Disease**

Intravenous ganciclovir has had a major impact on the mortality and morbidity of CMV disease in the transplant recipient (40, 41). Few would argue with the use of intravenous ganciclovir in this setting, although the only randomized placebo controlled trial, in bone marrow transplant patients with CMV gastroenteritis, did not show clinical benefit (42). Where there is fever and only trivial organ involvement, withdrawal of azathioprine or mycophenolate from a triple-drug regimen may be the only adjustment required to the baseline immunosuppression. More commonly, if the patient is unwell or there is evidence of organ dysfunction, it is appropriate to reduce (by 50%) the dose of calcineurin inhibitor.

Early concerns about neutropenia coincident with ganciclovir treatment have become less of an issue with greater experience and the appreciation that marrow suppression is often due to CMV disease and responds to antiviral therapy (43, 44).

Intravenous administration of ganciclovir remains the route of choice when the patient is seriously unwell, or when oral drug absorption is uncertain or poorly tolerated. However, oral valganciclovir was of equal efficacy to intravenous ganciclovir for treating CMV disease in a mixed group of solid organ transplant recipients, three quarters of whom were renal transplant recipients (45). Substantial clinical experience in recent years has re-enforced that this is an appropriate treatment strategy, which has the advantage of being able to offer outpatient management for a proportion of patients.

Very high doses of intravenous hyperimmune globulin (0.5 g/kg body weight) have been used in conjunction with ganciclovir for the treatment of pneumonitis (46). It is not possible to evaluate the effectiveness of this treatment from the published literature, but the treatment is unlikely to have serious side effects and should be considered for life (or sight)-threatening disease.

The optimal duration of intravenous treatment after resolution of clinical signs is uncertain. Serial PCR of CMV DNA offers an objective measure of the degree of viremia and may help to guide the duration of treatment. In practice, the clinical response and PCR measurements are used and, at least 2 weeks full-dose treatment is recommended, with a longer duration of treatment if there is not a prompt fall in viral load (7).

There is a significant risk of relapse after successful treatment of CMV disease, with recurrent CMV disease reported in various organ recipients (47–49). In one study, in kidney and kidney/pancreas recipients, relapse was seen in approximately one third of patients after treatment of the initial episode with ganciclovir (50). The quantitative measurement of CMV viral load may allow the risk of relapse to be predicted (50). Secondary prophylaxis after treatment of disease is common practice, but deciding the duration of treatment is difficult. In general, prophylactic dose antiviral therapy is usually prescribed for 1 month after resolution of CMV disease following mild illness, and for 3 months after severe illness, although there are no randomized trials to inform this strategy (7).

**Drug-Resistant CMV**

Although viral resistance has been rarely reported in the transplant literature (51–53), this may reflect underreporting because of difficulties with the required cell culture assays. When PCR is used, between 5% and 20% drug resistance has been reported in solid organ transplant recipients (54, 55).

The intensity of immunosuppression is likely to play a part in the frequency of drug resistance. However, in the VICTOR study, the greatest risk for recurrent DNAemia was not drug resistance itself, but failure to clear virus from the plasma by day 21 (56).

In clinical practice, viral resistance is manifest by progressive disease despite full-dose antiviral therapy or a static or increasing viral load after drug treatment. Importantly, viral load is not a reliable indicator of drug resistance in the first weeks of treatment (57) because the natural kinetics of CMV replication before antiviral treatment mean that patients with a rapidly increasing viral load are more likely to show a transient increase in viral load in the first 5 to 7 days after therapy, before a decline is observed. This means that if the patient is recovering then increasing viral loads do not confirm a diagnosis of drug resistance.

Despite recent advances in technology, phenotypic assays are technically difficult and have a slow turnaround time. Although important for setting reference standards, especially for novel mutations of unknown significance, they are not practical to guide clinical care. However, genotypic assays can relatively rapidly detect gene mutations that are associated with both high- and low-grade resistance to ganciclovir, and mutations that confer various degrees of resistance to ganciclovir, foscarnet, and cidofovir (58).

Although there is no evidence beyond that of anecdotal clinical experience, the use of high-dose hyperimmune CMV globulin is likely to be at least safe (46) and its effectiveness (if
any) presumably uninfluenced by drug-resistant mutations. However, it is not recommended as a single agent.

Cidofovir is a potential second-line therapy unless there is a UL54 genotype that confers both ganciclovir and cidofovir resistance (59). It has significant side effects including nephrotoxicity.

Foscarnet is reserved as second- or even third-line therapy partly because of significant risks of nephrotoxicity and electrolyte disturbances, especially an acute reduction in ionized calcium. There is a smaller risk of neurotoxicity, particularly grand mal convulsions. However, there is extensive clinical experience of the agent, mostly for treating patients with AIDS. It remains a valuable option in the presence of virus resistant to ganciclovir (60, 61). In high-risk clinical situations, consensus advice is to use combination treatment with ganciclovir and foscarnet (7).

There is some in vitro evidence that both sirolimus and leflunomide have an anti-CMV effect. Clinical anecdotes, which must be subject to publication bias, have indicated benefit from leflunomide in some cases (62, 63), but failure (in hemopoietic transplantation) in another (64). In general, mammalian target of rapamycin inhibitors seem to be associated with a reduction in CMV infection/disease (65), although it is likely that this may be secondary to their effects on CMV-specific T cells rather than by a direct antiviral effect. For the future, novel anti-CMV agents are in development, with maribavir and benzimidavir the most advanced (66, 67). The ability to restore CMV-specific T cells to the patient would also be highly attractive. There have been some research reports documenting the potential feasibility of transfer; however, this is likely at first to be only an option in hemopoietic transplantation (68).

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REFERENCES


