Canadian Society of Transplantation Consensus Workshop on Cytomegalovirus Management in Solid Organ Transplantation Final Report

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The Canadian Society of Transplantation sponsored a Cytomegalovirus (CMV) Consensus Working Group that met on March 19, 2003. The objectives of this group were to determine the current burden of CMV-associated disease in the setting of solid organ transplantation in Canada, make recommendations regarding optimal strategies for the diagnosis, treatment and prevention of CMV infection and disease, highlight gaps in knowledge and outline priorities for research and other initiatives that might further reduce the burden of CMV-associated effects in this setting. This report summarizes the recommendations of the working group including ratings of the strength of evidence supporting the recommendations.

Key words: Cytomegalovirus, Solid organ transplantation

On March 19, 2003, the Canadian Society of Transplantation (CST) sponsored a Cytomegalovirus (CMV) Consensus Working Group that met in Lake Louise, Alberta, Canada. The objectives of this group were to determine the current burden of CMV-associated disease in the setting of solid organ transplantaiton in Canada, make recommendations regarding optimal strategies for the diagnosis, treatment

and prevention of CMV infection and disease highlight gaps in knowledge and outline priorities for research, and other initiatives that might further reduce the burden of CMV-associated effects in this setting. Many of the members of this working group also participated in the development of guidelines for the diagnosis, prevention and treatment of infectious complications after solid organ transplantation by the American Society of Transplantation (AST) Infectious Disease Community of Practice (1). We have attempted to ensure consistency between these two sets of recommendations and those previously published by the International Herpes Management Forum (2). This report summarizes the recommendations of the Canadian CMV Consensus Working Group. The strength of evidence supporting the recommendations is recorded and weighted using the rating system recommended by the Infectious Diseases Society of America (IDSA) as shown in Table 1 (3).

What Is the Current Burden of CMV-Associated Disease in Canada and What Are the Risk Factors for its Development?

The risk factors for the development of CMV disease have been extensively studied (reviewed by Paya and Razonable (4)). Donor (D) and recipient (R) CMV serostatus are extremely important in determining risk, with immunologically naïve patients at risk for primary infection (D−R+) having greatest risk. Risk is also dependent on the type of organ transplanted, independent of immunosuppressive protocol used. Individual immunosuppressive agents have been associated with increased risk of disease, (steroids, OKT-3 and polyclonal anti-lymphocyte globulins), no increased risk (cyclosporine and tacrolimus) or conflicting data with respect to risk (mycophenolate mofetil). Risk associated with newer agents such as sirolimus and IL2 receptor antibody are unknown. The overall intensity of immunosuppression appears to be more important in determining risk than the use of any specific immunosuppressive agent. Other factors such as patient age and immunomodulatory factors associated with HLA matching, retransplantation and the use of cadaveric versus living-related donors also influence risk.

Table 1: Rating system

Evidence-based rating system used to determine strength of recommendations

Category	Definition	Recommendation
A	Strong evidence for efficacy and substantial clinical benefit	Strongly recommended
B	Strong or moderate evidence for efficacy, but only limited clinical benefit	Generally recommended
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches	Optional
D	Moderate evidence against efficacy or for adverse outcome	Generally not recommended
E	Strong evidence against efficacy or of adverse outcome	Never recommended

Evidence-based rating system used to determine quality of evidence supporting recommendation

I	Evidence from at least one well-executed randomized, controlled trial	
II	Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled	
	Analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments	
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees	

Source: Adapted from CDC. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1999; 48(RR-10): 1–66.

Data from multicenter clinical trials of CMV prophylaxis in specific organ transplant recipient groups, or in patients at highest risk (D+/R−) provide information regarding the residual burden of CMV viremia and disease that would be expected in these settings. However, significant data gaps with respect to the residual burden of CMV disease exist when this issue is examined, stratified by age, across all organ types, in lower risk patients and in the setting of specific immunosuppressive regimens. Data are also limited in settings where preemptive strategies are used for CMV disease prevention. Historically, the absence of clear and standardized definitions of CMV latency, CMV infection and CMV disease makes interpretation of the literature difficult including reports of disease incidence. Standardized definition of the types of CMV disease and grading of disease severity are lacking. Recent analyses from a Canadian transplant center suggest that CMV disease occurs in 5–16% (risk dependent on serostatus and organ transplanted) and 6% of adult and pediatric transplant recipients, respectively (personal communication, A Humar and U Allen).

In the past, the priority for CMV management has focused on preventing and treating invasive disease or the 'direct effects' of CMV infection (Figure 1) (2,4). However, there is increasing evidence that CMV may have significant 'indirect effects' in solid organ transplant recipients (Figure 1) (reviewed in 2). How these indirect effects might differ in adult and pediatric populations has not been explored as data from pediatric populations, with the exception of PTLD effects, are limited.

CMV infection/disease has been associated with acute rejection (renal transplantation) (5,6) and chronic graft dysfunction (including cardiac transplant vasculopathy and bronchiolitis obliterans syndrome in lung transplantation) (7,8). CMV is associated with cirrhosis and graft failure after liver transplantation and with more aggressive relapse

of hepatitis C with fibrosis. CMV is immunosuppressive, increasing the risk of opportunistic superinfections, particularly those due to fungi (9). CMV may also work synergistically with other agents to cause disease (Epstein–Barr virus and post-transplant lymphoproliferative disorders, viral syndromes and graft loss with human herpesvirus 6 and 7 (HHV-6 and HHV-7). CMV disease also appears to be an independent risk factor for patient and graft survival. Thus, the residual CMV disease burden in the era of preventative strategies must include the impact of indirect effects of infection.

Recommendations

(i) Uniform, standardized, practical definitions should be developed and used to define CMV infection and disease [AIII]. Definitions of CMV infection should take into account the sensitive nature of new diagnostic tests. It is recommended that CMV disease be defined using a modification of the system proposed by Ljungman et al. (10). The terms probable and definite should be used in case definitions of CMV diseases outlined in Table 2.

(ii) Prospective multi-center cohort studies using standardized case definitions for infection and disease as well as perhaps serial standardized viral load monitoring are required to determine the residual CMV disease burden [AIII]. Analyses should be stratified for donor/recipient serostatus, type of organ transplanted, immunosuppression protocol used and CMV prevention strategy (preemptive versus universal prophylaxis). Data are particularly lacking for pediatric populations and for some organ groups (lung, intestine, pancreas). Risk factors for residual disease risk should be sought in order to appropriately target and evaluate additional prevention strategies.

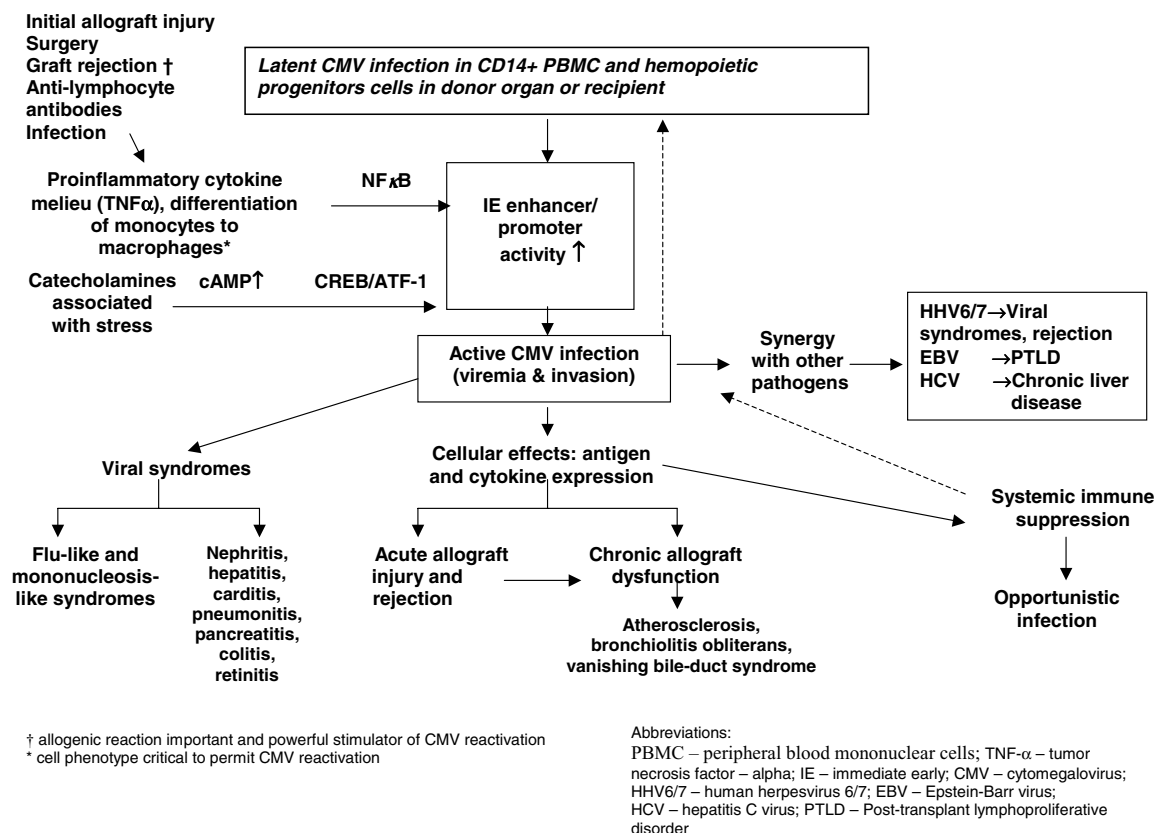(iii) It is recommended that clinical trials of new immunosuppressive agents or types of transplantation

† allogenic reaction important and powerful stimulator of CMV reactivation
* cell phenotype critical to permit CMV reactivation

Abbreviations:
PBMC – peripheral blood mononuclear cells; TNF-α – tumor
necrosis factor – alpha; IE – immediate early; CMV – cytomegalovirus;
HHV6/7 – human herpesvirus 6/7; EBV – Epstein-Barr virus;
HCV – hepatitis C virus; PTLD – Post-transplant lymphoproliferative
disorder

Modified from: ref. 24

Figure 1: Effects of cytomegalovirus: overview.

include the evaluation of CMV infection and disease [AIII]. In this context, standardized definitions of CMV infection and disease should be used along with standardized serial peripheral blood CMV viral load monitoring (see below), if possible. This would allow for more accurate determination of the impact of new regimens on the direct and indirect effects of CMV infection.

(iv) The introduction of universal leukodepletion of blood products in Canada in 2000 should have significantly reduced and perhaps eliminated transfusion-acquired CMV infection in solid organ transplant recipients. It is recommended that the effect of this intervention be documented in the transfused D−R− subgroup [BIII].

How Should CMV Infection/Disease Be Diagnosed?

Adequate laboratory support is essential for the appropriate management of CMV disease. Results must be delivered to clinicians in a timeframe that can impact patient care (ideally within 24 h for specimens submitted for disease diagnosis). Although serology is important for the deter-

mination of pre-transplant serostatus, it is of limited value for the diagnosis of acute infection. Similarly, viral cultures are generally too slow and insensitive to be very useful for acute diagnostic purposes; viral culture is best used on tissue biopsy and bronchoalveolar lavage (BAL) specimens. Viral cultures from lungs, tissue specimens and urine may reflect secretion or the presence of viremia and are often positive in the absence of true, invasive disease. Isolates from these samples, plasma or urine can also be useful for antiviral susceptibility testing. Histopathologic examination of tissue is important in diagnosing tissue invasive disease and morphologic analysis is made more sensitive by the use of immunohistochemistry and/or in situ hybridization to identify CMV-infected cells.

'CMV viral load' measured in peripheral blood (plasma, whole blood or peripheral blood mononuclear cells are all used) provides an extremely useful, although imperfect, assessment that measures the net effect of factors promoting CMV reactivation and replication counterbalanced by the CMV immune response. Viral load can be used as a surrogate marker of risk. Trends are more useful than individual assay results as the rate of rise of viral load as well as initial quantitative viral load assessment are independent indicators of CMV disease risk (11). Thus

Table 2: Definitions of cytomegalovirus (CMV) disease in solid organ transplant recipients

Disease type	Probable	Definite
CMV syndrome	One or more of the following: (i) Fever > 38°C (ii) New or increased malaise (iii) Leukopenia (iv) ≥5% atypical lymphocytes (v) Thrombocytopenia (vi) Elevation of hepatic transaminases transaminases (ALT or AST) to 2 × upper limit of normal (applicable to non-liver transplant recipients) plus evidence of CMV in blood by viral culture, antigenemia or a DNA/RNA-based assay	Clinical and laboratory findings as in 'probable' case and no other cause of symptoms/signs identified
Pneumonia[a]	Signs and/or symptoms of pulmonary disease in the absence of other documented cause plus evidence of CMV in blood and/or[c] bronchoalveolar lavage (BAL) fluid by viral culture, antigenemia or a DNA/RNA- based assay	Signs and/or symptoms of pulmonary disease plus detection of CMV in lung tissue by immunohistochemical analysis or *in situ* hybridization[d] with or without evidence of CMV in blood by viral culture, antigenemia or a DNA/RNA-based assay
Gastrointestinal disease	Symptoms of upper or lower gastrointestinal disease in the absence of other documented cause plus macroscopic mucosal lesions on endoscopy with or without evidence of CMV in blood or biopsy tissue by viral culture, antigenemia or an RNA/DNA-based assay	Symptoms or signs of upper or lower gastrointestinal disease plus detection of CMV in gastrointestinal tissue by immunohistochemical analysis or *in situ* hybridization[d] with or without evidence of CMV in blood by viral culture, antigenemia or an RNA/DNA-based assay
Hepatitis	Elevation of bilirubin and/or hepatic enzymes in the absence of other documented cause of hepatitis[b] plus evidence of CMV in blood or biopsy tissue by viral culture, antigenemia or a DNR/RNA-based assay	Elevation of bilirubin and/or hepatic enzymes plus detection of CMV in liver tissue by immunohistochemical analysisor *in situ* hybridization[d]
CNS disease	CNS symptoms in the absence of other documented cause plus evidence for CMV in CSF samples by viral culture assay	CNS symptoms plus detection of CMV in CNS tissue by immuno-histochemical analysis or DNA-based or *in situ* hybridization[d]
Retinitis	Not applicable	Lesions typical of CMV retinitis must be confirmed by an ophthalmologist
Other tissue invasive disease (nephritis, cystitis, myocarditis, pancreatitis, etc.)	Evidence of organ dysfunction in the absence of other documented cause[b] plus evidence of CMV in blood or biopsy tissue by viral culture, antigenemia or DNA/RNA-based assay	Symptoms/signs of organ dysfunction plus detection of CMV in affected tissue by immunohistochemical analysis or *in situ* hybridization[d]

[a]Superinfection or co-infection with other pathogens may occur and should be noted when present.
[b]If affected organ is the allograft, acute rejection must be excluded as a cause for the clinical symptoms.
[c]The detection of CMV in *both* BAL and peripheral blood strengthens the evidence for probable CMV pneumonitis.
[d]Although, immunohistochemistry and in situ hybridization techniques are more sensitive for the detection of CMV-infected cells than morphologic examination, the presence of typical cytomegalovirus inclusions should be considered evidence of definite disease.
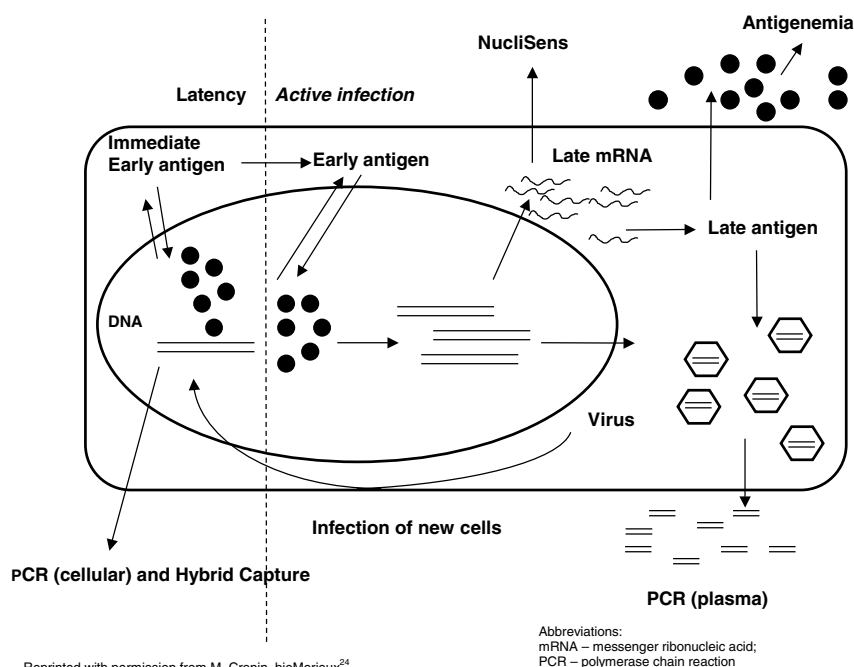Adapted from reference Ljungman et al. (10).

Figure 2: Detection targets for cytomegalovirus assays.

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Abbreviations:
mRNA – messenger ribonucleic acid;
PCR – polymerase chain reaction

determination of 'CMV viral load' is the key diagnostic tool used for the management of CMV disease (reviewed by Razonable et al.) (12).

Historically, the CMV pp65 antigenemia assay had been the 'gold standard' assay for this purpose. The CMV pp65 antigenemia assay remains a valuable test for centers managing small numbers of specimens. However, the need for a large sample volume, subjective interpretation that leads to poor standardization and precision, the need to process samples within 6–8 h of collection and the labour intensive, low throughput nature of the test, has led to many laboratories moving towards commercial and 'in house' (developed within the laboratory) molecular alternatives for CMV viral load assessment. These assays target detection of CMV DNA directly using signal amplification or amplification of CMV DNA or late CMV mRNA (Figure 2).

CMV viral load assays have significant potential power for patient surveillance if preemptive approaches are used, disease diagnosis and monitoring of treatment. However, the current assays also have serious limitations. CMV disease, particularly in the gastrointestinal tract and lung, can occur in the absence of a detectable viral load in peripheral blood. The lack of standardization and cross-referencing of these assays must be addressed. Although assay commercialization is a possible solution to this problem, current options are associated with high cost, relatively slow time to result determination and are not amenable to high throughput. Studies of PCR-based assays have used a variety of specimen types including whole blood, leukocytes, and plasma, with significant variability of results among specimen types. For quantitative CMV DNA assays there

is a lack of independent, external reference standards and proficiency testing, making it difficult to determine intralaboratory variability. Small changes in quantitative CMV DNA levels should be interpreted with caution as current assays cannot reliably differentiate differences in viral load levels that are less than 3–5 fold. Natural history studies to determine CMV viral load levels that are predictive of disease and can serve as trigger points for implementing antiviral therapy are limited, and ideally should be determined for each assay type and organ transplant group. The majority of natural history studies to date have used antigenemia assays and older and differing immunosuppressive regimens (reviewed in (2)).

Recommendations
(i) Serologic methods are useful in defining donor and recipient serostatus and post-transplant risk. Serologic assays, including the CMV-specific IgM assay, are not appropriate for diagnosis in the majority of cases [DII]. Documentation of seroconversion in R− patients may be useful at 6 months after transplant to determine residual risk of late-onset CMV disease, for management and counseling or to document possible transfusion-acquired infection in D−R− patients [BIII].

(ii) CMV viral load assays have clinical utility and should be available to all transplant programs [AIII]. pp65 antigenemia assays, and quantitative CMV DNA assays are acceptable methods for use [AII]. Although molecular-based detection of CMV DNA in leukocytes is more sensitive than its detection in plasma or whole blood, from a laboratory logistical perspective, whole blood or plasma samples are preferred for these assays [BIII]. Results of clinical

trials validating the utility of pp67 mRNA assays are awaited.

(iii) Standardization of CMV viral load assays is essential [AIII]. Canada may have a unique opportunity in this regard. Because of the regionalization of transplant programs and the relatively small number of laboratories providing transplant support, it is recommended that a center (or few centers of excellence) be identified in Canada and their best assay/approach be adopted in hospitals or regional centers. Proficiency testing to ensure maintenance of standardization should be implemented.

(iv) Multi-center studies are needed to validate the clinical utility of standardized molecular assays for use in triggering preemptive therapy, disease diagnosis and antiviral therapy monitoring [AIII]. Natural history studies are needed to link CMV viral load determinations with prediction of disease; such studies will allow investigation of optimal strategies for antiviral therapy for each assay type and organ transplanted.

How Should Ganciclovir-Sensitive CMV Disease Be Treated?

Ganciclovir, foscarnet and cidofovir have therapeutic benefit for CMV disease treatment. However, clinical experience with ganciclovir along with evidence for the nephrotoxicity of the latter two agents when combined with calcineurin inhibitors, make ganciclovir the preferred first-line agent. Appropriate drug dosing is important as sub-therapeutic drug levels in the face of high viral loads promotes resistance. Most of the 15–35% of CMV disease recurrence documented reflects incomplete suppression of viral replication rather than drug resistance. D+R− serostatus, multi-system disease and treatment of rejection have been identified as risk factors for recurrence. Patients who relapse have significantly higher initial CMV viral load, lower rates of CMV clearance and were significantly more likely to have CMV viral load detectable in peripheral blood or plasma at the end of therapy (13,14).

Recommendations

(i) Intravenous ganciclovir is recommended as the 'gold standard' for CMV disease treatment (5 mg/kg q 12 h) [AII]. Dosage should be adjusted carefully and promptly for renal impairment. Clinicians should avoid, when possible, dose reduction for leukopenia; consider the use of G-CSF as an alternative approach [BIII]. Oral ganciclovir or acyclovir should *not* be used for treatment [DII]. Based on pharmacokinetic data, valganciclovir might be used in place of intravenous IV ganciclovir but studies to validate this approach are required [CIII]. The benefit of routinely adding CMVIG to an antiviral or combining two antiviral drugs such as ganciclovir and foscarnet in this setting is uncertain [CII].

(ii) Adjunctive CMVIG is recommended by some experts in the setting of severe CMV disease (pneumonitis, severe gastrointestinal disease), or when the patient is hypogammaglobulinemic [BIII].

(iii) Immunosuppression should be reduced if possible [AIII]. How long immunosuppression should remain reduced is unclear. Efforts should be made to minimize immunosuppression as return to usual target levels of immunosuppressive drugs may promote recurrence.

(iv) Laboratory monitoring of CMV viral load during therapy should be performed to document resistance and monitor response [AII]. Initial monitoring should occur at 1 week after treatment onset. Treatment should continue for at least 1 week after CMV viral load is documented to be undetectable.

(v) The risk versus benefit of secondary prophylaxis after treatment is uncertain [CIII]. If secondary prophylaxis is used, viral load monitoring is essential to detect development of resistance. Oral valganciclovir therapy is equivalent to oral ganciclovir in this setting and may be preferred based on pharmacokinetic data [BIII], notwithstanding the uncertain benefit of secondary prophylaxis, as mentioned above.

How Should Ganciclovir-Resistant CMV Disease Be Treated?

Ganciclovir-resistant CMV disease is an emerging concern in solid organ transplantation. Its incidence, risk factors for its emergence and treatment outcomes are still being determined (15). Resistance should be suspected when stable or rising viral loads or persistence of clinical symptoms are observed 1 week or more after receipt of appropriate full-dose intravenous antiviral therapy. Levels of antigenemia often rise in the first several days after initiation of antiviral therapy when the pp65 antigenemia assay is being used to monitor viral load. This should not be interpreted as resistance. Resistance occurs predominantly in the D+R− subgroup. Resistance is a particular problem in lung and kidney-pancreas recipients although others are also at risk. Phenotypic resistance testing is the gold standard but it has a long turnaround time, is labor-intensive, costly and may underestimate true resistance rates. Genotypic resistance testing is more practical although identification of an unknown mutation is more problematic. UL97 (kinase) gene mutations are most common, confer low levels of ganciclovir resistance and do not demonstrate cross-resistance to other agents in contrast to less frequent UL 54 (DNA polymerase) mutations that result in high levels of ganciclovir resistance and may confer cross-resistance to other agents.

Recommendations

(i) Genotypic resistance testing should be made available to transplant centers in Canada through centralized testing facilities [AIII].
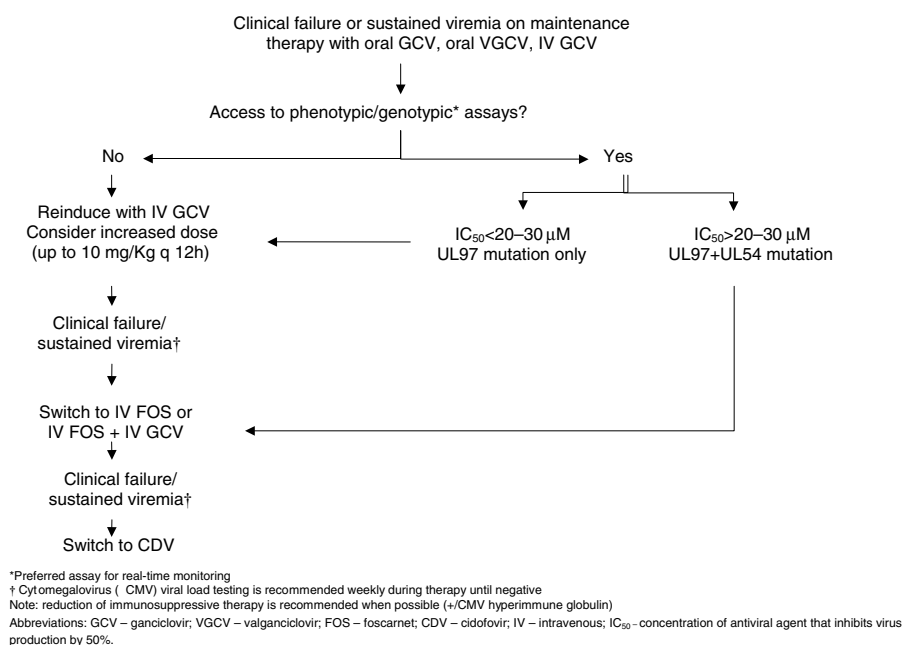
Clinical failure or sustained viremia on maintenance
therapy with oral GCV, oral VGCV, IV GCV

↓

Access to phenotypic/genotypic* assays?

No ← ——— → Yes

Reinduce with IV GCV
Consider increased dose
(up to 10 mg/Kg q 12h)

$IC_{50}<20–30\,\mu M$
UL97 mutation only

$IC_{50}>20–30\,\mu M$
UL97+UL54 mutation

Clinical failure/
sustained viremia†

Switch to IV FOS or
IV FOS + IV GCV

Clinical failure/
sustained viremia†

Switch to CDV

*Preferred assay for real-time monitoring
† Cytomegalovirus (CMV) viral load testing is recommended weekly during therapy until negative
Note: reduction of immunosuppressive therapy is recommended when possible (+/CMV hyperimmune globulin)
Abbreviations: GCV – ganciclovir; VGCV – valganciclovir; FOS – foscarnet; CDV – cidofovir; IV – intravenous; IC_{50} - concentration of antiviral agent that inhibits virus production by 50%.

Figure 3: Treatment of ganci-clovir-resistant cytomegalo-virus (CMV) infections.

(ii)   Management of CMV-resistant infections requires a multidisciplinary approach that should include an ID consultant and a pharmacist [AIII]. The recommended approach is summarized in Figure 3. In the absence of rapidly available genotypic resistance testing, if ganciclovir-resistant disease is suspected clinically using CMV viral load testing (note caution above in interpreting pp65 antigenemia when this assay is used for monitoring viral load) and the patient is not critically ill, reinduction with IV ganciclovir is recommended as initial therapy [AII]. Higher than normal doses of ganciclovir for reinduction (up to 10 mg/kg q 12 h) with careful monitoring for toxicity are used at some centers. G-CSF therapy is often required to treat the neutropenia associated with the high-dose ganciclovir therapy. Immunosuppression should be reduced, if possible, and consideration given to the use of adjunctive CMVIG therapy [BIII]. If CMV viral load remains stable or increases 1 week after initiation of reinduction therapy, alternative therapies should be considered. These may include reduced dose intravenous foscarnet combined with reduced dose intravenous ganciclovir therapy (reduces toxicity of both drugs) or full dose foscarnet alone (16) [AII]. Cidofovir therapy should be considered if other alternatives fail [BIII]. CMV viral load monitoring should occur weekly while the patient is on therapy; therapy should be continued for at least 1 week after viral load becomes undetectable [BIII].

How Can CMV Disease Be Prevented?

Two common strategies are employed for prevention of CMV disease: universal prophylaxis, (the administration of antiviral therapy for a defined period of time to all patients in populations considered at risk), and preemptive therapy (the administration of antiviral therapy in response to laboratory triggers such as specific CMV viral load assessments). Although the administration of antiviral therapy in response to clinical triggers such as the use of induction and rejection therapy is also referred to as preemptive therapy, some experts suggest that the term 'selective prophylaxis' better defines this approach. There are advantages and disadvantages to all these approaches (17–19). Universal prophylaxis has the benefit of preventing reactivation of other herpesviruses and does not require a laboratory assay to define risk. However, prolonged antiviral drug exposure may facilitate the development of drug resistance although this risk appears to be small. Drug toxicity and the occurrence of late CMV disease are other disadvantages of universal prophylaxis. Both selective prophylaxis and the preemptive approach reduces antiviral drug use and its associated cost and toxicity. However, the preemptive approach is logistically demanding, requiring strict compliance with often costly surveillance regimens and requires the availability of a highly predictive test for the early identification of patients at risk. This logistic limitation has been documented in some studies, especially in the setting of rapid viral replication in the D+/R− recipient, leading to the occurrence of CMV disease cases prior to identification of risk and deployment of preemptive intervention even when assays employing nucleic acid amplification were used for surveillance. Although preemptive approaches may reduce the risk of the emergence of antiviral resistant CMV, drug resistance has also been observed with prolonged preemptive therapy. All these strategies are effective for the prevention of CMV disease. The approach chosen must consider issues related to the individual patient, donor-recipient CMV

Table 3: Guidelines for CMV prevention in solid organ transplant recipients

Organ/CMV serostatus group; Donor (D), Recipient (R)	Relative merits of universal prophylaxis, preemptive therapy	Recommendations/options when applying universal prophylaxis
Kidney, liver, pancreas, heart D+/R−	• Universal prophylaxis preferred over preemptive therapy as rapid rise in viral load in absence of previous immunity makes preemptive strategies logistically difficult	• Oral ganciclovir (3 g/day) [A1] • Valganciclovir (900 mg/day) [A1]^a • IV ganciclovir (5 mg/kg per day) – kidney [A1], other organs [BII] • Valacyclovir (8 g/day) is an alternative in kidney transplant recipients [A1]
Kidney, liver, pancreas, heart R+	• Either universal prophylaxis or preemptive therapy are acceptable options • Some centers will choose to observe low risk patients (i.e. D−/R+ not receiving induction or reflection therapy) clinically and not use a prevention strategy	• Oral ganciclovir (3 g/day) [A1] • Valganciclovir (900 mg/day) [BII]^a • Valacyclovir (8 gm/day) (kidneys) [A1] • IV ganciclovir (in hearts, 4 weeks of therapy may be used) [A1]
Lung, heart-lung D+R−	• In this high-risk group, universal prophylaxis is preferred rather than preemptive therapy	• IV ganciclovir (5 mg/kg per day or 3× week) [BIII] • Valganciclovir (900 mg/day) [B11] • Some centers add CMV IG [CII] • Some centers extend prophylaxis to 6 months [BII]
Lung, heart-lung R+	• Universal prophylaxis is preferred rather than preemptive therapy	• IV ganciclovir [BII] • Valganciclovir (900 mg/day) [BII] • Oral ganciclovir (3 g/day) [BII] • Some centers add CMV IG in high-risk patients

^aSee details of US FDA caution in text.

serostatus, type of transplant, graft function and center resources.

Although there are a large number of reports of trials and retrospective reviews of experience with prophylactic and preemptive therapy (reviewed by Paya and Razonable (4), and IHMF (2)), there are relatively few large multi-center randomized trials evaluating specific drug regimens and prevention strategies. Interpretation of data is made difficult by non-standardized definitions of disease and infection, laboratory procedures and immunosuppressive regimens. It is also not clear that data from one type of organ transplant can be extrapolated to others.

Universal Prophylaxis

Recommendations
(i) Acyclovir and CMVIG are less effective than other oral and intravenous antiviral drugs such as oral valacyclovir, ganciclovir and valganciclovir and intravenous ganciclovir and should not be used as single agents for prophylaxis [DII].
(ii) Organ and serostatus specific recommendations for adult recipients are summarized in Table 3. Usual doses of drugs used for prophylaxis are as follows: IV ganciclovir (5 mg/kg per day), oral ganciclovir (3 g/day), or valganciclovir 900 mg/day. High dose valacylolovir (8 g/day) is effective in preventing CMV

disease in renal transplant recipients [A1]. The recommended duration of prophylaxis is 12–14 weeks unless otherwise specified. Data on appropriate drug dosing for ganciclovir and valganciclovir and their efficacy as prophylactic agents are not available in children. IV ganciclovir remains the current standard for CMV chemoprophylaxis in this population. The influence of CMV prophylaxis on indirect CMV effects is unknown and merits investigation.

(iii) In a randomized trial of valganciclovir versus oral ganciclovir in D+/R− transplant recipients, similar rates of CMV disease were seen in the two arms. However, in a subgroup analysis by the US FDA, there was a suggestion of a higher incidence of tissue-invasive disease in liver recipients receiving valganciclovir, although the number of events was quite low in both arms. This has led to a US FDA caution advising against the use of valganciclovir in D+/R− liver transplant recipients. However, some experts still use and recommend valganciclovir for this patient population [BIII]. In Canada, valganciclovir is approved for all organ groups.

(iv) Although single center studies suggest that graft vasculopathy was reduced in cardiac transplant recipients by the addition of CMVIG to oral ganciclovir (6), the benefit of routine addition of CMVIG to antiviral prophylaxis on direct and indirect effects of CMV infection is uncertain [C11].

(v) Routine viral load monitoring in kidney, heart, liver and pancreas is unnecessary while receiving primary prophylaxis; breakthrough events are rare [BII]. Routine surveillance may be indicated in lung transplant recipients where breakthrough events are more common [BII]. Although analysis of viral load monitoring in the double blind randomized controlled trial of valganciclovir versus oral ganciclovir prophylaxis in D−R+ suggested that post-prophylaxis monitoring of adult patients did not predict recurrent disease and the frequency of monitoring during this period was low (20). The benefit of frequent (weekly) CMV viral load monitoring for 2–3 months after discontinuation of prophylaxis to predict patients at risk of CMV disease is uncertain [CII].

(vi) Randomized control trial data are limited or lacking for lung, pancreas, intestinal and pediatric transplant recipients. Multi-center collaborative trials in these populations are encouraged [AIII].

Preemptive Therapy/Selective Prophylaxis

Significantly, less data are available to evaluate preemptive strategies. Lack of laboratory assay standardization and limited natural history studies that define trigger points for intervention are of concern in implementing this strategy. There are no randomized comparisons between effective prophylactic and preemptive strategies.

Recommendations

(i) Preemptive therapy is most appropriate for patients at low or intermediate risk for CMV disease [BII]. Universal prophylaxis rather than preemptive therapy is the recommended strategy in high risk patients (D+/R−).

(ii) Standardized viral load assays should be used. The optimal frequency of monitoring is unknown, but once weekly during the greatest period of risk (first 12 weeks after transplant) is recommended [BII].

(iii) The optimal drug regimen for preemptive therapy in response to a positive viral load is unknown. IV ganciclovir (5 mg/kg q12 h) has been successfully used for this purpose [BII]; the role of oral valganciclovir (900 mg b.i.d.) should be validated in clinical trials [BIII]. Although oral ganciclovir has been used in this setting, it is not recommended since in patients with high viral load, disease breakthrough has been observed, and the risk of developing drug resistant CMV disease is believed to be increased (21). Drugs should be continued for at least 1 week after CMV viral load is undetectable [BII]. IV ganciclovir is the drug of choice for use in pediatric populations (22).

(iv) It is recommended that selective prophylaxis (2 weeks of IV ganciclovir or valganciclovir (in therapeutic doses)) be given in response to clinical triggers (induction or rejection therapy with monoclonal or polyclonal anti-lymphocyte globulin) [BIII] (reviewed by IHMF (2)).

What Are the Costs Associated with CMV Infection and Disease in Solid Organ Transplantation?

Direct costs attributable to CMV are difficult to ascertain but appear to be significant. Regardless of organ and serostatus, patients acquiring CMV infection in the first year of transplantation have a documented increase in direct medical charges of 40–80% above baseline transplant costs. Indirect consequences of CMV infection are being increasingly recognized, are likely to be significantly greater than direct costs and have not been carefully examined. Treatment and prevention regimens for CMV are expensive and associated with some toxicity. Economic analyses with accurate cost-effectiveness data are limited as reviewed by IHMF (2,4,23).

Recommendations

(i) Accurate cost analysis during prospective studies of CMV prevention and treatment strategies are necessary and strongly recommended [AIII].

(ii) Decision analytical models that attempt to capture organ specific direct and indirect costs should be utilized if actual costs are not available for study [AIII].

Conclusion

The past two decades have seen significant advances in our understanding of the pathogenesis of CMV infection and disease and the far-reaching consequences of viral infection in solid organ transplantation. New antiviral agents and new laboratory tools have impacted patient morbidity and mortality through better treatment and prevention strategies. Data are lacking in several areas including those relating to pediatric patients. It is important to learn lessons from our transplant colleagues evaluating immunosuppressive regimens regarding the power of standardizing definitions and laboratory tools and using collaborative multi-center trials to improve patient outcomes. Similar approaches are needed in order to reduce the residual burden of CMV infection in the setting of solid organ transplantation.

Acknowledgment

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