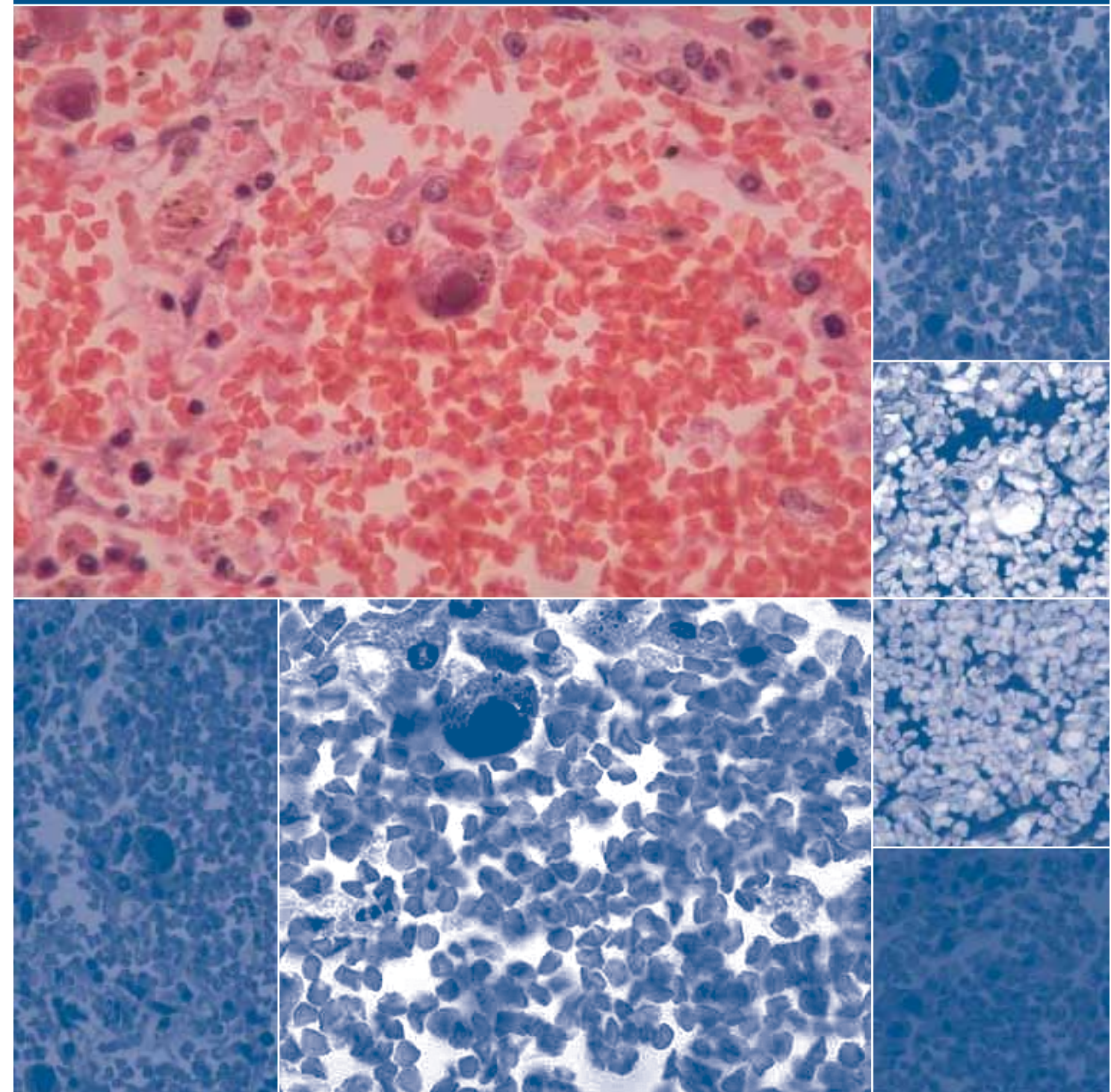




# Guidelines for the prevention and management of cytomegalovirus disease after solid organ transplantation

2nd edition 2004



Published by the British Transplantation Society  
Triangle House, Broomhill Road, London SW18 4HX  
Tel: 020 8875 2430 Fax: 020 8875 2435  
Email: [secretariat@bts.org.uk](mailto:secretariat@bts.org.uk) Web: [www.bts.org.uk](http://www.bts.org.uk)  
ISBN 0-9542221-3-X

Designed and produced by indigo 020 8858 5100

# Guidelines for the prevention and management of cytomegalovirus disease after solid organ transplantation



Published by the British Transplantation Society  
 Triangle House, Broomhill Road, London SW18 4HX  
 Tel: 020 8875 2430 Fax: 020 8875 2435  
 Email: secretariat@bts.org.uk Web: www.bts.org.uk  
 ISBN 0-9542221-3-X

Designed and produced by indigo 020 8858 5100

## Contents

<b>Recommendations</b>	<b>02</b>
For prophylaxis	02
For treatment	03
<b>Drug availability</b>	<b>03</b>
<b>Need for guidelines</b>	<b>04</b>
<b>Process of writing</b>	<b>05</b>
<b>Biology of CMV in man</b>	<b>06</b>
<b>The Diagnosis of CMV Infection and Disease</b>	<b>07</b>
<b>Frequency of CMV and consequences of disease in immunosuppressed solid organ transplant recipients</b>	<b>08</b>
Frequency of CMV in immunosuppressed solid organ transplant recipients	08
Cytomegalovirus and early allograft dysfunction	08
Cytomegalovirus and late graft rejection	09
Cytomegalovirus and graft survival	10
Cytomegalovirus and patient survival	10
<b>Prevention of CMV disease</b>	<b>11</b>
CMV matching	11
Vaccination	11
Passive immunoprophylaxis	11
Interferon	11
Conventional Prophylactic anti-viral drug therapy	11
– Aciclovir	11
– Valaciclovir	12
– Ganciclovir	12
– Valganciclovir	13
Pre-emptive anti viral prophylaxis	14
<b>Treatment of CMV disease</b>	<b>16</b>
<b>Suggested audit standards</b>	<b>17</b>
<b>Statements of potential conflicts of interest</b>	<b>18</b>
<b>References</b>	<b>19</b>

# Recommendations

Evidence is presented using the principles adopted by the Canadian Task Force on the Periodic Health Examination.<sup>1</sup> The recommendations, depending on the strength of the evidence, are graded using categories A through E. The strongest recommendations (grade A, in support of the preventative intervention, or grade E, against the use of the intervention) are given only if the intervention is supported by or negated by high quality studies, usually type I randomized controlled studies. Grade B and D recommendations are given when there is less convincing evidence, usually from cohort or other nonrandomized controlled studies (type II evidence). Data from randomized controlled studies believed to be susceptible to bias or methodologic concerns were given the same weight as type II studies. Grade C recommendations indicate that there is insufficient or contradictory evidence either against or for the intervention in question. In this situation, the clinician should base their treatment on individualized clinical criteria.

## For prophylaxis

CMV seronegative recipients who receive a solid organ transplant from a donor who is seropositive should be offered prophylaxis against primary infection. The same should apply where the donor and recipient are both sero-positive and the patient is treated with ATG/ALG/OKT3.

### For renal transplant recipients

The recommended prophylactic strategy is one of:

- a) Valaciclovir for ninety days post transplant (Grade A)
- b) Oral ganciclovir for ninety days post transplant (Grade A)
- c) Intra-venous ganciclovir for 28 days (Grade A)
- d) Oral valganciclovir for 100 days (Grade A)
- e) High dose oral aciclovir for 12 weeks (Grade B)
- f) Intermittent intravenous CMV hyperimmune globulin for 12 weeks (Grade B)
- g) Serial measurements of viral load with treatment with intra-venous ganciclovir or oral valganciclovir when levels predict disease (Grade B)

- h) Serial measurements of viral load with treatment with oral ganciclovir when levels predict disease (Grade A)

### For liver transplant recipients

The recommended prophylactic strategy is one of:

- a) Oral ganciclovir for ninety days post transplant (Grade A)
- b) Intra-venous ganciclovir for 100 days (Grade A)
- c) Oral valganciclovir for 100 days (Grade A)
- d) Valaciclovir for ninety days post transplant (Grade C)
- e) Serial measurements of viral load with treatment with intra-venous ganciclovir or oral valganciclovir when levels predict disease (Grade A)

### For kidney / pancreas transplant recipients

The recommended prophylactic strategy is one of:

- a) Oral ganciclovir for ninety days post transplant (Grade C)
- b) Intra-venous ganciclovir for 28 days (Grade C)
- c) Oral valganciclovir for 100 days (Grade C)
- d) Valaciclovir for ninety days post transplant (Grade C)
- e) Serial measurements of viral load with treatment with intra-venous ganciclovir when levels predict disease (Grade C)

### For lung transplant recipients

The recommended prophylactic strategy is one of:

- a) Oral ganciclovir for ninety days post transplant (Grade B)
- b) Intra-venous ganciclovir for 28 days then oral ganciclovir for 60 days (Grade B)
- c) Valaciclovir for ninety days post transplant (Grade C)

### For heart transplant recipients

The recommended prophylactic strategy is one of:

- a) Oral valganciclovir for 100 days (Grade A)
- b) Oral ganciclovir for ninety days post transplant (Grade B)
- c) Intra-venous ganciclovir for 28 days (Grade B)
- e) Valaciclovir for ninety days post transplant (Grade C)
- e) Serial measurements of viral load with treatment with intra-venous ganciclovir when levels predict disease (Grade C)

Where donor and recipient are both sero-positive and the patient is not treated with ATG/ALG/OKT3.

### For renal transplant recipients:

No prophylaxis is recommended (Grade A)

### For liver transplant recipients:

No prophylaxis is recommended (Grade A)

### For renal / pancreas transplant recipients:

No prophylaxis is recommended (Grade C)

### For lung transplant recipients:

The recommended prophylactic strategy is one of:

- a) Oral ganciclovir for ninety days post transplant (Grade C)
- b) Intra-venous ganciclovir for 28 days then oral ganciclovir for 60 days (Grade C)
- c) Valaciclovir for ninety days post transplant (Grade C)

### For heart transplant recipients:

No prophylaxis is recommended (Grade C)

## For treatment

Patients with CMV disease should as a first line receive intra-venous ganciclovir or oral valganciclovir for at least 14 days (Grade B)

Foscarnet and cidofovir are usually second line therapeutic options unless ganciclovir resistance has been demonstrated (Grade C)

Consideration should be given to reduction in immunosuppression (Grade C)

## Drug availability

In the autumn of 2003 as this document was being revised Roche announced that they intended to stop manufacturing oral ganciclovir. In the United Kingdom supplies of this drug are expected to last until spring 2004. Specific dosing recommendations have not been addressed in this document, but prescribers will be aware of the need for careful dose titration in paediatric practice and when patients have severely impaired renal function if valganciclovir is substituted for ganciclovir.

We have decided not to alter the recommendations in this document to reflect current drug availability. In part this is because of the volume of literature relating to oral ganciclovir use and the possibility in the future of the manufacture of a generic product.

## Need for guidelines

The management of CMV disease post transplantation has been comprehensively reviewed by others (for example<sup>2</sup>). Guidelines were published in 1998 focusing on adult patients undergoing renal transplantation<sup>3</sup>. More current are guidelines regarding post renal transplant care recently published by the European Dialysis and Transplant Association which included the management of CMV disease<sup>4</sup>. Guidelines in development relating to solid organ transplant recipients are available on [www.IHMF.org](http://www.IHMF.org)

## Process of writing

A group was invited by Mr A.Bakran (Consultant Vascular and Transplant Surgeon, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP) on behalf of the Council of the British Transplant Society to prepare guidelines for the management of CMV disease after solid organ transplantation. The first draft was written by Dr. C.G.Newstead (Consultant Renal Physician, St.James's University Hospital, Leeds LS9 7TF) in Spring 2001 after a systematic review of the literature using retrieval from electronic databases and reading suggestions from colleagues. Major revisions were made by Prof. P.D. Griffiths (Professor of Virology, Royal Free Hospital and University College Medical School, London NW3 2QG) and less extensive revisions by: Dr. J.G. O'Grady (Consultant Hepatologist, Institute of Liver Studies, Kings College Hospital, London SE3 9RS), and Dr J.K. Parameshwar (Consultant Cardiologist Transplantation, Papworth Hospital, Papworth Everard, Cambridgeshire CB3 8RE).

In the summer and autumn of 2003 at the request of the BTS Council the document was revised, principally by Dr. C.G.Newstead and Prof. P.D. Griffiths. Drs J.G. O'Grady and J.K. Parameshwar approved the final version which was first made available on the BTS website in November 2003 for two months to allow revisions to be suggested by colleagues. This version was re-written taking account the majority of the (modest) number of contributions in January 2004.

## Biology of CMV in man

Cytomegalovirus is one of the herpes group of viruses which are widely distributed among mammals. The various strains of CMV are species specific and produce a cytopathic effect resulting in greatly enlarged (cytomegalic) cells containing cytoplasmic and intranuclear inclusions. As is typical for the herpes class of viruses, primary infection results in the most severe disease. After primary CMV infection the viral genome enters monocytes and remains latent. Re-infection with a different human strain can occur, as can reactivation of the latent viral infection. Re-infection usually results in less serious disease than the primary infection. Reactivation may be provoked by immunosuppression due either to another disease, such as carcinoma or AIDS, or treatment with immunosuppressive or chemotherapeutic agents, and is usually clinically benign. The prevalence of antibody indicating previous infection increases with age in all human populations that have been studied. The prevalence of past exposure to CMV, as indicated by a positive IgG, varies markedly throughout the world and is close to 100% in adults in many developing countries such as the Philippines and Uganda<sup>5</sup>.

In the developed world the percentage of the population who are seropositive increases roughly linearly with age and is approximately 40% at age 20 and 80% at age 60<sup>6,7</sup>.

Transmission occurs from direct person-to-person contact. As the virus is labile intimate exposure to saliva, urine, breast milk or genital secretions, has to occur and the risk of transmission to Health Care Workers is very low. Although congenital CMV infection only rarely leads to typical disease, with hepatosplenomegaly, jaundice, microcephalae, prematurity, choroidoretinitis, petechiae, mental retardation and hearing loss it is an important health care burden. Perinatal infection is more common but clinically benign. In the immunocompetent child or adult most commonly the primary infection is sub-clinical. Malaise, fever and myalgia are the most frequent symptoms with biochemical hepatitis and atypical lymphocytes found on investigations.

## The Diagnosis of CMV Infection and Disease

In the past there has been considerable difficulty in transplant recipients discriminating between latent CMV infection and CMV disease. Given the primary infection, latent infection and re-activation cycle seen with herpes virus this is not surprising. The detection of the classic large cells in culture takes several weeks and so is of little practical clinical use. As well as the symptoms detailed in the section "CMV Infection in Transplant Patients" routine blood tests may detect bone marrow suppression, especially of the white cell series, as well as biochemical hepatitis. After a primary infection an individual would be expected to mount IgM and later an IgG immunoglobulin response against CMV. It is the presence of the latter, which is used to determine prior exposure of both donors and recipients to CMV infection. In the immunosuppressed the antibody rise may be delayed or absent and the delay in the serological change makes these tests at best only of use for retrospective diagnosis. A new recombinant antigen-based cytomegalovirus immunoglobulin M immunoassay has recently been reported. Although the new assay was sensitive for CMV specific IgM, in a group of liver transplant recipients the IgM was only found before detection of the virus when the recipient was seropositive prior to transplantation. In this setting the assay had a very low positive predictive value<sup>8</sup>.

Early antigen fluorescent fixation tests rely on the detection of CMV generated antigen in cells in urine or alveolar macrophages obtained from direct lavage. As with all fluorescein techniques, subjective interpretation is problematic and false positive results are seen<sup>9</sup>. CMV p65 antigen in circulating polymorphonuclear leucocytes in the buffy coat may discriminate between infection and disease, but again subjective interpretation and poor reproducibility, particularly when delay occurs in the processing of specimens, present problems<sup>10</sup>. The rapid detection of CMV was first made possible using the shell viral assay, but the sensitivity of the technique proved to be inadequate<sup>11</sup>. Tests based on the polymerase chain reaction carried out on plasma, whole blood or leucocytes are much more sensitive. In the early days of using this technique, technical problems with contamination and inhibition, as well as the lack of standardisation between laboratories, had to be overcome<sup>12</sup>.

Increased experience and the availability of commercial assays have now allowed PCR diagnosis to be offered on a more routine basis<sup>13,14</sup>. Other methods such as hybrid capture for CMV DNA are also being evaluated.

On occasions it is necessary to prove CMV organ specific dysfunction by obtaining a biopsy. This can be especially useful if co-infection with another organism is possible or if another cause of allograft dysfunction, such as rejection, is within the differential diagnosis as is often the case. Liver, native and allograft, bone marrow, lung, renal allograft and gastrointestinal biopsies can be diagnostic. The usual clinical approach is to choose to biopsy an organ that is demonstrating clear dysfunction balancing the risk of the diagnostic procedure against the likelihood of an unequivocal result. CMV is a systemic infection and histological diagnosis may be achieved from unlikely sites<sup>15</sup>.

Histopathology may be specific for CMV disease by identifying CMV inclusion bodies, or suggestive as in the detection of 'microabscesses' in the parenchyma in CMV hepatitis. In either event, histopathology is insensitive compared to PCR<sup>16</sup>. The detection of CMV inclusions in an organ biopsied because of characteristic symptoms and signs meets the internationally agreed case definition of "CMV disease"<sup>17</sup>. The objective of modern management is to avoid patients reaching such an overt clinical endpoint.

# Frequency of CMV and consequences of disease in immunosuppressed solid organ transplant recipients

## Frequency of CMV in immunosuppressed solid organ transplant recipients

This varies markedly depending on the definition of CMV disease that is used and the intensity of immunosuppression. Approximately 8% of renal, 29% of liver, 25% of heart and 39% of heart/lung transplants can be considered to experience symptomatic CMV infection<sup>18</sup>.

Primary infection with CMV typically occurs approximately four to six weeks post-transplantation in a sero-negative individual who receives a seropositive organ. The symptoms due to primary disease may occur as early as 20 days and are rare more than 50 days post-transplantation provided the patient has not received antiviral drugs<sup>19</sup>. Many symptoms such as fever, night sweats, fatigue and myalgia are non-specific. Retinitis can be pathognomonic, but it is rarely seen in the transplant population. Respiratory distress noticed at first on exercise is a sinister symptom and measurement of oxygen saturation and blood gas analysis, the former at both rest and exercise, can give an early clue to pulmonary involvement. Gastrointestinal disease with diarrhoea, abdominal pain and nausea is relatively frequent. One group has suggested that epigastric pain that decreases in the supine position is a symptom uniquely seen in CMV gastritis<sup>20</sup>. Symptomatic adrenal insufficiency is most unusual, probably because transplant recipients often receive supra-physiological doses of corticosteroids.

The severity of CMV disease in the era before effective anti-viral treatments can be evaluated from relatively few publications. A 30% death rate in sero-negative recipients of seropositive kidneys who received ALG has been reported<sup>18</sup>. Although taking into account the proviso regarding the definition of CMV disease already mentioned, there is modest recent literature about the impact of CMV disease in transplant units. An economic analysis of the impact of CMV disease in liver transplant recipients demonstrated that CMV disease was associated with a 49% increase in costs and that effective antiviral prophylaxis was associated with an overall reduction in costs in the CMV sero-negative recipient CMV seropositive donor combination<sup>21</sup>. An audit from

Manchester UK showed that 30% of renal recipients were high risk and half of these experienced disease. An average of eight in-patient days per 'at risk' patient were spent managing CMV disease post-transplant<sup>22</sup>. The frequency of disease among the positive recipients of positive kidneys and positive recipients of negative kidneys was extremely low. In a recent publication describing liver transplant recipients who did not receive antiviral prophylaxis, 8 out of 9 donor positive/recipient negative (D+R-) and 7 out of 17 donor negative/recipient positive (D-R+) patients developed CMV disease<sup>8</sup>.

Because of the multiple human strains of CMV, seropositive organ recipients are at risk of re-infection with a different strain of virus<sup>23</sup>. In this situation, the clinical syndrome is usually less severe than in primary infection and the onset of disease is often delayed to approximately three months post-transplantation. Seropositive recipients of sero-negative grafts (and sero-negative blood products) can develop CMV disease due to reactivation of latent virus. This is usually mild compared to primary infection and also often delayed to approximately three months post-transplantation. Leucodepleted or filtered whole blood has a very low risk for transmission of CMV disease<sup>24</sup>.

## Cytomegalovirus and early allograft dysfunction

CMV infection may decrease cell-mediated immunity, reducing the T-helper to suppressor cell ratio as well as the ability of T-cells to produce interferon- $\gamma$ . This may allow coincident infection with other viral, bacterial, protozoal or fungal organisms. Despite the immunosuppressive effects of acute CMV disease, it has long been recognised that CMV infection can be coincident with acute allograft rejection<sup>25</sup>. Prophylaxis with Valaciclovir reduced biopsy-proven acute graft rejection by 50% in the D+R- subgroup of renal transplant recipients<sup>26</sup> although the mechanisms involved are not defined. CMV increases the expression of major histocompatibility (MHC) class I and II molecules on both vascular endothelial and tubular epithelial cells which are targets for renal allograft rejection. The mechanism may be via the production of interferon- $\gamma$  by T-cells<sup>27,28</sup> as well as the increased expression of MHC molecules. Another mechanism

of enhanced rejection may be the fact that CMV encodes a molecule similar to MHC class I antigens and there is some homology between the immediate early region protein of CMV and some class II antigens. As well as these effects, which would be expected to enhance the alloantigen dependent rejection, CMV infection by increasing co-stimulatory molecules on antigen presenting cells, vascular endothelial cells, tubular epithelial cells and T-lymphocytes would be expected to enhance the alloantigen independent pathway of rejection<sup>29,30</sup>. Elevated anti-endothelial cell antibodies and IL-2 levels have been reported in a small group of renal and cardiac allograft recipients coincident with CMV infection. This may indicate an increased humoral response to endothelial, antigens which the authors postulated could be a risk factor for both vascular and chronic rejection<sup>31</sup>.

There has been considerable interest regarding the potential role of CMV infection in both native coronary and cardiac allograft atherosclerosis. In 60 histological specimens of re-stenoses after native coronary angioplasty 38% were found to have accumulated a high amount of tumour suppressor protein p53 and this correlated with the presence of CMV in the lesions. Furthermore, smooth muscle cells from the re-stenoses grew a CMV protein IE84 that in cell culture inhibited p53 function and the authors suggested this mechanism may have contributed to the relapse<sup>29</sup>. In the rat aortic allograft model (of chronic vascular rejection), it has been known for some time that early infection with rat CMV doubled the rate of smooth muscle proliferation and arteriosclerotic alterations in the intima. Late infection had almost no effect<sup>30</sup>. In this model immunosuppression had a protective (rather than detrimental) effect on vascular wall histology<sup>32</sup>. In a whole organ model in the rat CMV significantly enhanced the development of renal chronic allograft rejection<sup>33</sup>. In other experiments, again in the rat allograft model, treatment with Ganciclovir blocked the early adventitial inflammation and reduced smooth muscle cell proliferation<sup>34</sup>.

A *post-hoc* analysis of a subset of a randomised placebo controlled study reviewed 149 consecutive heart transplant patients who received either intravenous ganciclovir or placebo for the initial 28 days after transplantation<sup>35</sup>. The patients

underwent annual arteriography. Twenty-eight could not be evaluated, mostly because of early death. The rest had a mean follow up of 4.7 years. The actuarial incidence of transplant coronary artery disease was 43% versus 60% in the ganciclovir treated and control groups, respectively. One of the independent risk factors for coronary artery disease was no Ganciclovir treatment (relative risk 2.1, confidence interval 1.1-5.3,  $p = 0.04$ ). The report has considerable limitations, as the authors emphasise, in that it was not designed to address the specific question explored in this paper. Despite the intriguing *in vivo* animal and human data, there is apparently inconsistent *in vitro* work showing that the induction of cell surface adhesion molecules after CMV infection is not influenced by ganciclovir<sup>36</sup>.

A study of 60 liver transplant recipients having at least four blood specimens for PCR analyses showed that CMV and HHV6 was associated significantly with acute graft rejection<sup>37</sup>. In a complex study, 242 consecutive renal transplants were prospectively followed, including 157 with and 85 without CMV infection<sup>38</sup>. The latter group were randomly paired with 85 of the infected patients and given matched dates for fictitious CMV infections. The outcome was that the incidence of acute rejection after CMV infection was higher among those infected patients (45% versus 11%).

## Cytomegalovirus and late graft rejection

A clinical study predating the availability of effective antiviral therapy found a strong association between CMV infection (rather than disease) and chronic rejection after liver transplantation<sup>39</sup>. Two other studies strongly linked CMV hepatitis and failure to clear CMV from the liver with chronic rejection<sup>40,41</sup>. However, no difference in the incidence of chronic rejection was found during the first year after liver transplantation in a large multicentre study of oral ganciclovir prophylaxis<sup>19</sup>. The significance of this observation has been questioned by some authorities on the basis of the short period of follow-up.

In a series of 301 heart transplant recipients 91 showed serological evidence of CMV infection and graft atherosclerosis was more frequent and earlier in this group. Ninety percent of the non-CMV patients were free of angiographically severe

## Frequency of CMV and consequences of disease in immunosuppressed solid organ transplant recipients

obstruction compared with 72% of the CMV patients<sup>42</sup>. In 128 heart transplant recipients who were transplanted between 1992 and 1993, all of whom received four weeks of intravenous Ganciclovir and then aciclovir early severe rejection was associated with CMV viremia (47 versus 16%) and tissue-invasive CMV (11 versus 0%). However there was no association between either symptomatic CMV or asymptomatic CMV on the subsequent development of allograft vasculopathy over the subsequent 6 to 7 years<sup>43</sup>. The potential impact of acute CMV disease on chronic vascular rejection will need examining further by prospective studies.

Large registry data, as well as single centre studies, demonstrate a reduced graft and patient survival, both in individuals who experience CMV disease and those who are at highest risk of primary infection. In the UNOS database, which includes over 47,000 patients, the renal graft survival disadvantage in the cohort whose donor was CMV seropositive was 4% at three years<sup>44</sup>. Some single centres have reported even more deleterious outcome<sup>45</sup>, but others have shown no such effect<sup>46</sup>.

### Cytomegalovirus and graft survival

An attempt was made to separate the impact of acute rejection and CMV disease on long term graft survival in a single centre study of 1339 renal transplant recipients. A multivariate analysis showed that CMV disease appeared to influence long term graft survival but only when coupled with the occurrence of acute rejection<sup>47</sup>.

In a liver transplant population of 33 patients receiving 57 transplants, persistent CMV infection as defined by serial PCR measurements was significantly associated with graft loss through chronic rejection. However, there was no significant correlation between primary infection or symptomatic disease and chronic rejection, possibly as a consequence of the small sample size<sup>48</sup>.

Interesting data with regard to the incidence of CMV infection on long-term outcome comes from a series of 1545 cadaveric renal transplant recipients divided historically into two groups on the basis of availability of ganciclovir. In the early group, the survival of the R-D+ patients was significantly poorer<sup>49</sup>. However, close inspection of the survival curves shows no change in late graft survival before and after the use of universal prophylaxis, arguing against a role for CMV infection causing late graft loss in renal transplantation.

### Cytomegalovirus and patient survival

Prophylaxis protects from early death in the high risk D+/R- group in the case of heart transplant recipients (about a 6% difference) and early death (about 1% difference) in the case of renal transplant recipients. Impressive data corroborating this is available from the Collaborative Transplant Society website, the address for which is <http://www.ctstransplant.org/>. No such effect is seen in liver transplantation in this registry. In lung transplantation the data is even more striking with CMV prophylaxis resulting in 95% versus 44% survival at three months in those who did and did not receive CMV prophylaxis<sup>50</sup>.

## Prevention of CMV disease

There has been considerable interest in developing an effective prophylactic strategy against this complication of solid organ transplantation because of the significant morbidity and mortality associated with CMV infection.

### CMV matching

CMV matching to avoid transplanting a sero-negative individual with a seropositive organ is an option. Given the life-sustaining nature of successful heart, lung and liver transplantation it is difficult to practise in these settings. However, prior to the advent of oral antiviral prophylaxis many units avoided transplanting CMV positive lungs into CMV negative recipients. In renal or pancreas transplantation it is an option that is most often exercised in the rare situation where there is more than one otherwise equally good candidate for a single organ. Another situation in renal transplantation where avoiding a donor positive recipient negative combination would be worth considering is in the situation where an unusual degree of immunosuppressive therapy would be predicted to be required, an example may be an ABO "incompatible" pair. Widespread adoption of CMV matching would disadvantage younger recipients in developed health care systems as they are more likely to be CMV negative and it could compromise HLA matching or other criteria that are currently used to determine allocation.

### Vaccination

One attractive option for prophylaxis would be vaccination. Early attempts using the Towne virus strain in renal transplant recipients were largely unsuccessful. Nine of the 37 sero-negative patients failed to produce antibodies. 71% of those transplanted in the placebo group developed CMV disease as compared with 56% in the vaccinated cohort<sup>51</sup>. There have been other studies in which the rate of CMV disease was decreased from approximately 50% to 37% and severe disease from 29% to 5% in the vaccinated patients<sup>52,53</sup>.

The heterogeneity of strains has limited the yield from vaccination as a prophylactic strategy. More recently vaccines directed against envelope glycoproteins have generated renewed interest

as these are well conserved between strains.

The biggest public health return would be achieved by vaccinating women prior to reproductive age<sup>54</sup>.

### Passive immunoprophylaxis

This has been explored in solid organ transplantation in a number of randomised trials<sup>55,56,57</sup>. However, only one in liver transplant recipients was placebo controlled<sup>56</sup>. This study randomised 141 patients and a third of these received OKT3. The hyperimmune globulin provided significant overall protection from severe disease. However, no protection was seen in the D+/R- sub-group. The combined studies are difficult to interpret because of the different proportion of high-risk patients in each study group and varying definitions of CMV disease. However, when the rate of CMV disease, as defined in each study, are compared in the treated and untreated groups, the results can be interpreted as demonstrating that intravenous immunoglobulin reduced the rate of CMV disease to approximately half of that seen in the placebo group. Intravenous treatment is generally less convenient for the patient or health care provider, and carries the theoretical risk of transmitting blood-borne viruses (or vCJD in the UK). However, it does have the advantage of allowing compliance to be documented and on occasions this may have significant advantages.

### Interferon

Interferon was shown to reduce CMV excretion in pilot studies, but unfortunately with little clinical benefit in renal transplant recipients<sup>58,59</sup>. This result was confirmed in a formal blinded placebo controlled study in renal transplant recipients<sup>60</sup>.

### Coventional Prophylactic anti-viral drug therapy

#### Aciclovir

Aciclovir was shown to reduce CMV disease to about one third, from 28% to 8% in a prospective placebo-controlled randomised clinical trial in renal transplantation with approximately 50 patients in

## Prevention of CMV disease

each arm<sup>61</sup>. In liver transplantation the results have been contradictory with some or no benefit seen<sup>62,63</sup>. Others have shown no benefit in renal transplantation when ATG/OKT3 was used<sup>64</sup>. Aciclovir may therefore only provide significant protection transplant recipients at lower risk, such as D+/R+ patients or where early immunosuppression is relatively modest for example in that small percentage of renal recipients who receive ciclosporin monotherapy. An alternative strategy used CMV hyperimmune globulin in combination with antiviral drugs, but the utility of this approach is difficult to assess as the study was uncontrolled<sup>65</sup>.

### Valaciclovir

This prodrug has a three to five fold improved oral bioavailability compared to aciclovir. Valaciclovir has been studied in a randomised prospective placebo controlled study in a renal transplant cohort of 208 D+/R- and 408 recipient positive renal transplant patients<sup>26</sup>. In the high risk D+/R- group, the incidence of CMV disease at 90 days was 45% in the placebo and 3% in the valaciclovir groups, respectively. Among the recipient positive patients, there was also a significant difference but at the low incidences of 6% and 0%, depending on whether or not the donor was positive. After six months, the incidence of CMV disease had increased to 45% among sero-negative recipients of the placebo and to 16% in the sero-negative recipients of valaciclovir. There was also a highly significant difference in the frequency of biopsy confirmed acute rejection with 26% of the valaciclovir group and the 52% of the placebo group in the D+/R- cohort experiencing rejection by six months.

### Ganciclovir

A variety of regimens using relative short courses of intravenous ganciclovir have been used<sup>66,67</sup>. Intravenous ganciclovir reduced the frequency of CMV disease to a quarter of that seen in the control group in a randomised blinded study<sup>68</sup>. Another randomised study compared intravenous ganciclovir for 100 days with aciclovir, initially intravenous and then high dose orally, for 100 days in liver transplant recipients and found that symptomatic CMV disease occurred in 0.8% of the ganciclovir and 10% of the aciclovir groups ( $p=0.002$ )<sup>69</sup>. In contrast, where the

degree of immunosuppression was more intense, as is typical in cardiac transplantation, intravenous ganciclovir for 28 days was shown in a placebo controlled randomised controlled trial not to be effective in the highest risk (D+/R-) sub-group 66. In this situation other strategies, such as the combination of antiviral drugs and CMV hyperimmune globulin or more protracted intravenous or oral drug therapy should be evaluated.

Despite the poor bioavailability of oral ganciclovir a prospective double blind placebo-controlled randomised trial in liver transplant recipients (only excluding donor and recipient sero-negative) showed that the drug reduced morbidity due to CMV disease to about a quarter of that seen in the placebo group. Total CMV disease was reduced from 19% to 5% ( $p < 0.001$ ), CMV syndrome from 12% to 4% ( $p = 0.006$ ) and tissue invasive CMV disease from 9% to 1% ( $p < 0.001$ )<sup>19</sup>. These data are consistent with the findings of a similar study of 42 renal transplant patients randomised to receive either ganciclovir or aciclovir and followed for six months. Again all except donor and recipient sero-negative were included but all patients bar one received quadruple induction therapy including ALG<sup>70</sup>.

155 D+/R- recipients of a variety of solid organs received five to ten days of intra-venous ganciclovir and then either oral ganciclovir or aciclovir for a further 12 weeks. Approximately one quarter was treated with antilymphocyte antibody therapy. There was no difference in the frequency of CMV disease but tissue invasive CMV disease was seen in 10 out of 78 in the aciclovir and 3 out of 77 in the ganciclovir group<sup>71</sup>. In a randomised prospective controlled trial of oral aciclovir versus oral ganciclovir in renal transplant recipients who received quadruple immunosuppression including OKT3, CMV disease occurred in the D+/R- subgroup in 5 of 13 receiving aciclovir and 0 of 14 receiving ganciclovir during the treatment phase. However, post-prophylaxis three patients in the ganciclovir group developed evidence of infection<sup>72</sup>.

A retrospective study compared 60 renal transplant recipients who had received oral ganciclovir with 70 who had received valaciclovir. There was no difference in the incidence of CMV infection in the two groups, 6.9% versus 5.4%<sup>73</sup>.

A variety of new antiviral drugs have been studied for efficacy against CMV disease. Some, such as cidofovir, have unwelcome side effects such as nephrotoxicity. However, in the setting of ganciclovir resistance the agent clearly may be of value<sup>74</sup>.

### Valganciclovir

Oral valganciclovir gives plasma ganciclovir levels similar to those achieved with intravenous therapy and 10 fold higher to those achieved with the oral formulation of ganciclovir. This represents a significant advance for both treatment and prophylaxis<sup>75</sup> although similar side-effects are expected. The drug has now been licensed in the United Kingdom with an indication which includes "for the prevention of CMV disease in CMV negative patients who have received a solid organ transplant from a CMV positive donor". The key data comes from a randomised double-blind multi-centre study which recruited 364 adult CMV negative recipients of CMV positive solid organ transplants. The recipients were randomised 2:1 to valganciclovir or ganciclovir prophylaxis. The randomisation was stratified among the organ types with 177 liver, 120 kidney, 11 kidney/pancreas and 56 heart transplant recipients recruited. Treatment started within 10 days of transplantation and continued until 100 days post-surgery. The data has at present been presented only in abstract form and recipients of lung or small bowel transplants were not included. 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% in the valganciclovir and 3.2% in the ganciclovir group<sup>76</sup>. The frequency of detectable viral load<sup>77</sup> and drug associated side effects was similar. At the end of the prophylactic period 198 valganciclovir treated and 103 ganciclovir treated patients were assessed for the presence of ganciclovir resistant CMV strains. The incidence was very low at 0% for the valganciclovir and 1.9% in patients who had received ganciclovir<sup>78</sup>.

All prophylactic strategies have disadvantages. To be effective they rely to a greater or less degree on good patient compliance. The treatments add to the cost of the procedure and are unnecessary for a proportion of individuals who receive them. The agents have a side effect profile that must be balanced against the

advantages of therapy. Although viral resistance has been rarely reported in the transplant literature<sup>79,80,81,82</sup> this may reflect under-reporting because of difficulties with the required cell culture assays. When PCR was used, 22% of 45 patients with AIDS receiving long term ganciclovir developed resistance<sup>83</sup> and a figure of 20% has recently been reported for solid organ transplant recipients<sup>84</sup>. The duration of therapy is likely to be important<sup>85</sup>. Ganciclovir resistance is shown in about 8% of patients with AIDS after three months' treatment<sup>85</sup> rising to 11% with resistant blood or urine CMV isolates at six months, and 28% at nine months<sup>87</sup>. The intensity of the immunosuppression is likely to play a part in the frequency of ganciclovir resistance. Six children with combined immunodeficiency developed ganciclovir resistant CMV within ten days to three weeks after starting treatment<sup>88</sup>. Finally, blanket prophylactic therapy has the potential to delay the onset, but not necessarily reduce the frequency of CMV disease. This is a particular problem in heavily immunosuppressed patient groups. An abstract reported that 3 months of ganciclovir treatment in a renal transplant population (70% of who had received ALG) that the rate of CMV disease was strikingly different at three months but was the same by the time both the groups had reached one year<sup>89</sup>.

## Prevention of CMV disease

### Pre-emptive anti viral prophylaxis

Because of the disadvantages of universal prophylaxis there has been considerable interest in pre-emptive prophylactic strategies. In this approach, patients undergo regular surveillance and are treated when judged to be at high risk of developing CMV disease, usually with intravenous ganciclovir. A variety of markers for predicting future CMV disease have been described such as the shell viral assay, PCR in serum, PCR from peripheral blood mononuclear cells, PCR from whole blood and antigenaemia. These have sensitivities which vary from 57% to approximately 85% and a specificity from about 35% to 90%. Results should be interpreted in terms of the rapid dynamics of CMV replication<sup>14,90</sup>. A publication, which showed the plot of the probability of CMV disease against viral load in a renal transplant population, is instructive<sup>91</sup>. At a viral load of 5 log<sub>10</sub> copies per ml the probability was 20%, at 5.5 50% and at 6 about 80%. Both of the molecular assays used predicted all cases of disease at a median time of about 12 days before the onset of symptoms. Others have used similar assays to reliably predict CMV disease in kidney / pancreas<sup>92</sup> and other solid organ recipients<sup>93,94</sup>. The absolute levels of viraemia that are recommended to give the threshold to start pre-emptive therapy will of course 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 viraemia compared to the Hybrid Capture Assay. Clearly the proportion of individuals who receive “unnecessary” pre-emptive treatment versus those who develop CMV disease because they are not offered pre-emptive therapy will depend on where the threshold is set. Ideally units should establish the clinical significance of their local assay.

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 large fraction of patients who did not necessarily require it. The authors reassuringly noted that none of the 29 patients who were continuously negative for CMV

PCR developed CMV disease. However, as a guide to treatment in this setting it seems somewhat limited<sup>95</sup>. In a British bone marrow transplant unit 7 of 10 CMV positive recipients of a CMV positive graft developed CMV DNAemia but only 3 went on to develop clinical disease requiring ganciclovir treatment. Of 11 low risk patients, CMV negative recipients of CMV negative grafts (who also received CMV negative blood products), 6 developed evidence of CMV DNAemia, although only one had clinical evidence of CMV disease. The authors report the source of the positive tests in these cases is unclear and emphasize the significant laboratory variation in expertise in this area<sup>96</sup>.

Several authors have reported on a prophylactic strategy that followed patients at risk with serial measures of CMV antigenaemia and then treated those predicted to be about to develop CMV disease with intra-venous ganciclovir. In a recent study on 71 liver transplant recipients, CMV antigenaemia occurred in 22 and these patients were randomised into two groups. One received intra-venous ganciclovir for seven days and the other oral ganciclovir for ten weeks. Although of low power because of the small sample size, it is striking that CMV disease was only seen in one patient (in the intra-venous treatment arm)<sup>97</sup>. Two different strategies were adopted in a study of renal transplant recipients who were CMV sero-positive at the time of transplantation. In one centre patients received oral ganciclovir for 12 weeks or until antigen negative for two consecutive weeks and in the other centre intra-venous ganciclovir for two weeks and then oral treatment until antigen negative for two consecutive weeks. Of 192 patients who met the study criteria 90 were treated. All patients cleared antigen and there were no relapses. The single case of tissue invasive CMV disease occurred in the intra-venous treatment group<sup>98</sup>.

Of 49 patients who received unrelated donor bone marrow transplants who and were either CMV seropositive or received a seropositive donor, 27 patients were enrolled in a pre-emptive strategy and 22 received prophylactic ganciclovir for four months. By one year the probability of CMV disease occurring was 64% and 30% in the pre-emptive prophylactic and ganciclovir groups, respectively (p=0.07)<sup>99</sup>.

A retrospective study of 39 renal, 28 liver and 23 heart transplant recipients noted 26 episodes of infection managed according to a pre-emptive strategy; 4 of these developed CMV disease but there were no deaths<sup>100</sup>. However, there were also 21 episodes “not managed according to the programme” where 12 individuals developed CMV disease and there were 2 deaths possibly related to CMV infection. This emphasises when a pre-emptive strategy is put in place it is most important that all the elements for monitoring it appropriately are available.

A recent randomised placebo-controlled trial in 69 liver transplant patients gave 8 weeks oral ganciclovir therapy when CMV DNA was detected by PCR<sup>101</sup>. CMV disease developed in 12% of placebo recipients compared to 0% of those receiving ganciclovir. This trial provides the evidence base for using pre-emptive therapy to control CMV disease in recipients of liver transplants.

In a study in renal transplant recipients 38 patients were evaluable from a group randomised to be monitored by CMVpp65 antigen tests, if a positive test was demonstrated the patients received oral ganciclovir and these were compared to a control group of 38 who received treatment if they developed disease. No patients in the pre-emptive group but nine in the control group developed CMV disease<sup>102</sup>.

The duration of pre-emptive anti-viral therapy is important. To our knowledge the optimum length has not been formally tested. Some authors have recommended a minimum period of four weeks<sup>102</sup>. It is logical to be guided by serial measurements of the viral load and others have recommended treatment continue for two to four weeks after the patient has tested negative for viral replication<sup>103</sup>.

The authors of a recent review, when discussing prophylaxis for CMV and solid organ transplantation, pointed out that “conventional prophylactic therapy has a large body of supportive controlled clinical studies demonstrating efficacy and cost-effectiveness<sup>104</sup>. The strategy also has the advantage of preventing other herpes viruses. There is some information to suggest that prophylactic therapy may benefit by reducing rejection”. The authors contrast pre-emptive 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 at the present

time purported benefits of pre-emptive therapy, such as decreased cost, fewer adverse medication effects and less antiviral resistance have not been proven in head to head clinical studies”. In the counterpoint article published side-by-side, the problems of prophylaxis were discussed<sup>105</sup>. 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 encouragement of drug resistance.

Clearly, both prophylaxis and pre-emptive therapy are effective at controlling CMV disease, but the choice between them is controversial. Colleagues should discuss the practicalities with their local virologists and audit their agreed management strategy.

## Treatment of CMV disease

Early references emphasise the need to reduce immunosuppression as well as giving specific antiviral therapy<sup>106,107</sup>. The former option is easier for renal rather than life-sustaining transplants. Intra-venous ganciclovir has had a major impact on the mortality and morbidity seen with this condition<sup>107,108,109,110</sup>. Few would argue with the use of intra-venous ganciclovir in this setting although the only randomised placebo controlled trial, in bone marrow transplant patients with CMV gastroenteritis did not show clinical benefit<sup>111</sup>. In the situation where there is fever and only trivial organ involvement, for the bone marrow for example this may be a white blood count lower than 3.0 withdrawal of Azathioprine or Mycophenolate from a triple drug regime may be all that is required. If the patient is unwell (as opposed to merely uncomfortable) or there is evidence of organ dysfunction, most commonly with significant marrow suppression, hepatitis, gastrointestinal ulceration or pneumonitis, it is appropriate to reduce (to about a half) the dose of calcinurin inhibitor and treat with intravenous ganciclovir. Early concerns about neutropenia coincident with its use have become less of an anxiety with greater experience and the appreciation that marrow suppression may be due to CMV disease and respond to ganciclovir therapy. This approach to treatment is in line with that recommended by others<sup>112,113,114</sup>. Very high doses of intravenous hyperimmune globulin (0.5 g/kg body weight) have been used for treatment of pneumonitis in conjunction with ganciclovir<sup>115</sup>.

The optimal duration of intravenous treatment after resolution of clinical signs is uncertain. In the future DNA PCR may offer an objective measure of the degree of viraemia and may help to decide the duration of treatment.

An important clinical point is the fact that infection with other co-pathogens in an immunosuppressed patient with CMV is common and other associated infections as well as CMV disease should always be ruled out by repeated clinical examination and special investigations. A decrease in the incidence of fungal infections was demonstrated in one sub-group of a randomised controlled trial of intravenous ganciclovir in cardiac transplant recipients<sup>116</sup>.

Following successful treatment of CMV disease there is a significant risk of relapse with recurrent CMV disease which has been reported for a variety

of organ recipients<sup>117,118,119,120,121,122</sup>. 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<sup>123</sup>. The quantitative measurement of CMV viral load may allow the risk of relapse to be predicted<sup>124</sup>.

Foscarnet is reserved as second line therapy partly because of significant risk of nephrotoxicity and electrolyte disturbances especially an acute reduction in ionised 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. The drug remains a valuable option in the presence of virus resistant to ganciclovir<sup>125,126</sup>.

Cidofovir is also reserved as second line therapy particularly in the presence of renal impairment. The drug is an option in the presence of virus resistant to other agents<sup>74</sup>.

## Suggested audit standards

The number of episodes of CMV disease diagnosed in the first year post transplantation should be collected and expressed as the number of episodes per transplant in the donor positive / recipient sero-negative group and in the donor negative or positive and recipient sero-positive group. This local data should be compared with current best practice as listed below.

CMV disease in solid organ recipients should be defined as an episode of ill health during which the patient experiences fever with another organ involvement such as bone marrow suppression, hepatitis, pneumonitis, transplant dysfunction, gastrointestinal tract involvement, or adrenalitis in a pattern typical for CMV induced dysfunction. Coincident with this it is necessary to demonstrate either typical histology, recovery of CMV from an affected organ or a diagnostic elevation in the quantity of circulating virus measured by molecular techniques or a diagnostic rise in subsequent paired CMV IgG and IgM titres.

Current practice results in a CMV disease rate in the first year of approximately 8% in donor positive / recipient sero-negative groups in renal transplantation<sup>3,26</sup>.

Current practice results in a CMV disease rate in the first year of approximately 4% in donor positive / recipient sero-negative groups in liver transplantation<sup>19,69</sup>.

Current practice results in a CMV disease rate in the first year of approximately 10% in donor positive / recipient sero-negative groups in kidney / pancreas transplantation<sup>127</sup>.

Current practice results in a CMV disease rate in the first year of approximately 15% in donor positive / recipient sero-negative groups in lung transplantation<sup>2,3,26,128,128</sup>.

Current practice results in a CMV disease rate in the first year of approximately 10% in donor positive / recipient sero-negative groups in heart transplantation<sup>66,129</sup>.

Current practice results in a CMV disease rate in the first year of approximately 15% in the donor sero-negative or positive / recipient sero-positive sub-group in lung transplantation<sup>2,3,26,128,129</sup>.

## Statements of potential conflicts of interest

Dr. C.G. Newstead has received honoraria for lectures and teaching as well as expenses for travel and accommodation to attend scientific meetings from Fujisawa, Novartis, Wyeth and Roche. He has received honoraria for contributions to Advisory Boards for both Roche and Wyeth. Since election to the Council of the BTS and Chair of the Standards Committee he has declined invitation to contribute to Advisory Boards. Research and that of close collaborators has been in part sponsored by the above named companies as well as eight different Foundations.

Prof. P. Griffiths. has received honoraria for lectures and teaching as well as expenses for travel and accommodation to attend scientific meetings principally from Glaxo, SmithKline and Roche. He has also received honoraria for contributions to Advisory Boards for Glaxo SmithKline, Roche and Wyeth.

Dr. J. O'Grady, has received honoraria (for advisory board work and lectures) and travel expenses for scientific meetings from Fujisawa and Roche.

Dr J. Parameshwar has received honoraria for lectures and teaching as well as expenses for travel to attend scientific meetings from Novartis and Roche. He has also received honoraria for contribution to advisory boards for Roche.

## References

- Canada Communications Group: *Canadian Guide to Clinical Preventative Health Care*, Quebec, Hull 1994
- Patel R, Snydman DR, Rubin RH, Ho M, Pescovitz M, Martin M, Paya CV *Cytomegalovirus prophylaxis in solid organ transplant recipients* Transplantation 1996; 61 (9): 1279-1289
- Jassal SV, Roscoe JM, Zaltzman JS, Mazzulli T, Krajden M, Gadawski M, Cattran DC, Cardella CJ, Albert SE, Cole EH *Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation* J Am Soc Nephrol 1998; 3: 1697-1708
- Berthous F, Abramowicz D, Bradley B, et al *European best practice guidelines for renal transplantation (Part 1)* Nephrology Dialysis Transplantation 2000; 15 (suppl 7): 71-74
- Krech U *Bulletin of the World Health Organisation* 1973; 49: 103-106
- Wentworth BB, Alexander ER *Sero epidemiology of infections due to members of the herpes virus group* Am J Epidemiology 1971; 94 (6): 496-507
- Griffiths PD, Baboonian C *A prospective study of primary cytomegalovirus infection during pregnancy: final report* Br J Obstet Gynaecol 1984; 91: 307-315
- Halling VW, Maine GT, Groettum CM, et al *Clinical evaluation of a new recombinant antigen-based cytomegalovirus immunoglobulin M immunoassay in liver transplant recipients* Transplantation 2001; 71 (3): 395-397
- Evans PC, Gray JJ, Wreghitt TG, Marcus RE, Alexander GJ *Comparison of three PCR techniques for detecting cytomegalovirus (CMV) DNA in serum, detection of early antigen fluorescent foci and culture for the diagnosis of CMV infection* J Med Microbiol 1999; 48 (11): 1029-1035
- Landry ML, Ferguson, S Cohen, K Huber, P Wetherill *Effect of delayed specimen processing on cytomegalovirus antigenemia test result* J Clin Microbiol 1995; 33: 257-259
- Pillay D, Charman H, Lok K, Griffiths PD *Detection of cytomegalovirus by a rapid culture system: a comparison of monoclonal antibodies in a clinical setting* J Virol Methods 1992; 40: 219-224
- Grundt JE, Ehrnst A, Einsele H, Emery VC, Hebart H, Prentice HG, Ljungman P *A three-center European external quality control study of PCR for detection of cytomegalovirus DNA in blood* J Clin Microbiol 1996; 34: 1166-1170
- Einsele H, Ehninger G, Hebart H, Wittkowski KM, Schuler U, Jahn G, et al *Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation* Blood 1995; 86: 2815-2820
- Emery VC, Sabin CA, Cope AV, Gor D, Hassan-Walker AF, Griffiths PD *Application of viral-load kinetics to identify patients who develop cytomegalovirus disease after transplantation* Lancet 2000; 355: 2032-2036
- Shutze WP, Kirklin JK, Cummings OW, Aldrete JS *Cytomegalovirus hemorrhoiditis in cardiac allograft recipients* Transplantation 1991; 51: 918-922
- Mattes FM, McLaughlin JE, Emery VC, Clark DA, Griffiths PD *Histopathological detection of owl's eye inclusions is still specific for cytomegalovirus in the era of human herpesviruses 6 and 7* Journal of Clinical Pathology 2000; 53: 612-614
- Ljungman P, Plotkin SA *Workshop of CMV disease: definitions, clinical severity scores, and new syndromes* Scandinavian Journal of Infectious Diseases - Suppl 1995; 99: 87-89
- Patel R, Snydman DR, Rubin RH, Ho M, Pescovitz M, Martin M, Paya CV *Cytomegalovirus prophylaxis in solid organ transplant recipients* Transplantation 1996; 61 (9): 1279-1289
- Gane E, Saliba F, Valdecasas GJ, O'Grady J, Pescovitz MD, Lyman S, Robinson CA *Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients.* The Oral Ganciclovir International Transplant Study Group Lancet 1997; 350 (9093): 1729-1733
- Giladi M, Lembo A, Johnson BL Jr *Postural epigastric pain: a unique symptom of primary cytomegalovirus gastritis?* Infection 1998; 26 (4): 234-5
- Kim WR, Badley AD, Wiesner RH, Porayko MK, Seaberg EC, Keating MR, et al *The economic impact of cytomegalovirus infection after liver transplantation* Transplantation 2000; 69: 357-361
- Newstead CG *Cytomegalovirus disease in renal transplantation* Nephrol Dial Transpl 1995; 10 (suppl 1): 68-73
- Grundt JE, Lui SF, Super M, Berry NJ, Sweny P, Fernando ON, Moorhead J, Griffiths PD *Symptomatic cytomegalovirus infection in seropositive kidney recipients: reinfection with donor virus rather than reactivation of recipient virus* Lancet 1988; 2 (8603): 132-135
- Sayers MH, Anderson KC, Goodnough LT, et al *Reducing the risk for transfusion-transmitted cytomegalovirus infections* Ann Intern Med 1992; 116: 55

- 25 Rubin RH  
*The indirect effects of cytomegalovirus infection on the outcome of organ transplantation*  
JAMA 1989; 261: 3607-3609
- 26 Lowance D, Neumayer HH, Legendre CM, Squifflet JP, Kovarik J, Brennan PJ, Norman D, Mendez R, Keating MR, Coggon GL, Crisp A, Lee IC  
*Valaciclovir for the prevention of cytomegalovirus disease after renal transplantation*  
International Valaciclovir Cytomegalovirus Prophylaxis Transplantation Study Group  
N Engl J Med 1999; 340 (19): 1462-1470
- 27 Arbustini E, Morbini P, Grasso M, Diegoli M, Fasani R, Porcu E, Banchieri N, Perfetti V, Pederzoli C, Grossi P, Dalla Gasperina D, Martinelli L, Paulli M, Ernst M, Plachter B, Vigano M, Solcia E  
*Human cytomegalovirus early infection, acute rejection, and major histocompatibility class II expression in transplanted lung. Molecular, immunocytochemical, and histopathologic investigations*  
Transplantation 1996; 61 (3): 418-427
- 28 Tuder RM, Weinberg A, Panajotopoulos N, Kalil J  
*Cytomegalovirus infection amplifies class I major histocompatibility complex expression on cultured human endothelial cells*  
J Heart Lung Transplant 1994; 13 (1 Pt 1): 129-138
- 29 Speir E, Modali R, Huang E, Leon MB, Shawl F, Finkel T, Epstein SE  
*Potential role of human cytomegalovirus and p53 interaction in coronary restenosis*  
Science 1994; 265: 391-394
- 30 Lemstrom KB, Bruning JH, Bruggeman CA, Lautenschlager IT, Hayry PJ  
*Cytomegalovirus infection enhances smooth muscle cell proliferation and intimal thickening of rat aortic allografts*  
J Clin Invest 1993; 92 (2): 549-558
- 31 Toyoda M, Galfayan K, Galera OA, Petrosian A, Czer LS, Jordan SC  
*Cytomegalovirus infection induces anti-endothelial cell antibodies in cardiac and renal allograft recipients*  
Transpl Immunol 1997; 5 (2): 104-111
- 32 Lemstrom KB, Bruning JH, Bruggeman CA, Lautenschlager IT, Hayry PJ  
*Triple drug immunosuppression significantly reduces immune activation and allograft arteriosclerosis in cytomegalovirus-infected rat aortic allografts and induces early latency of viral infection*  
Am J Pathol 1994; 144 (6): 1334-1347
- 33 Koskinen PK, Yilmaz S, Kallio E, Bruggeman CA, Hayry PJ, Lemstrom K  
*Rat cytomegalovirus infection and chronic kidney allograft rejection*  
Transpl Int 1996; 9 (suppl 1): S3-S4
- 34 Lemstrom KB, Bruning JH, Bruggeman CA, Koskinen PK, Aho PT, Yilmaz S, Lautenschlager IT, Häyry PJ  
*Cytomegalovirus infection-enhanced allograft arteriosclerosis is prevented by DHPG prophylaxis in the rat*  
Circulation 1994; 90: 1969-1978
- 35 Valantine H A, Gao SZ, Menon SG, Renlund DG, Hunt SA, Oyer P, Stinson EB, Brown BW, Merigan TC, Schroeder JS  
*Impact of prophylactic immediate posttransplant ganciclovir on development of transplant atherosclerosis*  
Circulation 1999; 100: 61-66
- 36 Craigen JL, Grundy JE  
*Cytomegalovirus induced up-regulation of LFA-3 (CD58) and ICAM-1 (CD54) is a direct viral effect that is not prevented by ganciclovir or foscarnet treatment*  
Transplantation 1996; 62: 1102-1108
- 37 Griffiths PD, Ait-Khaled M, Bearcroft CP, Clark DA, Quaglia A, Davies SE, Burroughs AK, Rolles K, Kidd IM, Knight SN, Noibi SM, Cope AV, Phillips AN, Emery VC  
*Human herpesviruses 6 and 7 as potential pathogens after liver transplant: prospective comparison with the effect of cytomegalovirus*  
J Med Virol 1999; 59 (4): 496-501
- 38 Pouteil-Noble C, Ecochard R, Landrison G, Donia-Maged A, Tardy JC, Bosshard, Colon S, Betuel H, Aymard M, Touraine JL  
*Cytomegalovirus infection – an etiological factor for rejection? A prospective study in 242 renal transplant patients*  
Transplantation 1993; 55 (4): 851-857
- 39 O'Grady JG, Alexander GJ, Sutherland S, Donaldson PT, Harvey F, Portmann B, Calne RY, Williams R  
*Cytomegalovirus infection and donor/recipient HLA antigens: interdependent co-factors in pathogenesis of vanishing bile-duct syndrome after liver transplantation*  
Lancet 1988; 2 (8606): 302-305
- 40 Lautenschlager I, Hockerstedt K, Jalanko H, Loginov R, Salmela K, Taskinen E, Ahonen J  
*Persistent cytomegalovirus in liver allografts with chronic rejection*  
Hepatology 1997; 25 (1): 190-194
- 41 Arnold JC, Portmann BC, O'Grady JG, Naoumov NV, Alexander G, Williams R  
*Cytomegalovirus infection persists in the liver graft in the vanishing bile duct syndrome*  
Hepatology 1992; 16(2): 494-496
- 42 Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE  
*Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis*  
JAMA 1989; 261 (24): 3561-3566
- 43 Avery RK, Mossad SB, Young JB, Goormastic M, Mawhorter SD, McCarthy PM  
*Long-term outcomes in heart transplant recipients who received ganciclovir prophylaxis: Impact of CMV and CMV serostatus on rejection, allograft vasculopathy, and survival*  
Transplantation 2000; 69 (8): S238
- 44 Hirata M, Terasaki PI, Cho YW  
*Cytomegalovirus antibody status and renal transplantation: 1987-1994*  
Transplantation 1996; 62 (1): 34-37

- 45 Ranjan D, Burke G, Exquenazi V, Milgrom M, Lokeilat N, Roth D, et al  
*Factors affecting the ten-year outcome of human renal allografts*  
Transplantation 1991; 51 (1): 113-117
- 46 Martin S, Morris D, Dyer PA, Gokal R, Mallick NP, Johnson RWG  
*The association between cytomegalovirus-specific antibodies, lymphocytotoxic antibodies, HLA-DR phenotype and graft outcome in renal transplant recipients*  
Transplantation 1991; 51: 1303-1305
- 47 Humar A, Gillingham KJ, Payne WD, Dunn DL, Sutherland DER, Matas AJ  
*Association between cytomegalovirus disease and chronic rejection in kidney transplant recipients*  
Transplantation 1999; 68 (12): 1879-1883
- 48 Evans PC, Soin A, Wreghitt TG, Taylor CJ, Wight DGD, Alexander GJM  
*An association between cytomegalovirus infection and chronic rejection after liver transplantation*  
Transplantation 2000; 69 (1): 30-35
- 49 Schneeberger H, Aydemir S, Muller R, Illner WD, Pfeiffer M, Theodorakis J, Zanker B, Land W  
*Hyperimmunoglobulin prophylaxis, monitoring and preemptive ganciclovir treatment eliminate the risk of CMV infection to improve patient and renal allograft survival*  
Transpl Int 2000; 13 (suppl 1): S354-S358
- 50 Bando K, Paradis IL, Komatsu K, Donishi H, Matsushima M, Keena RJ, Hardesty RL, Armitage JM, Griffith BP  
*Analysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation*  
J Thorac Cardiovasc Surg 1995; 109 (1): 49-57
- 51 Plotkin SA, Friedman HM, Fleisher GR, Dafoe DC, Grossman RA, Smiley ML, et al  
*Towne-vaccine-induced prevention of cytomegalovirus disease after renal transplants*  
Lancet 1984; 528-30
- 52 Plotkin SA, Higgins R, Kurtz JB, Morris PJ, Campbell Da Jr, Shope TC, Spector SA, Dankner WM  
*Multicenter trial of Towne strain attenuated virus vaccine in sero-negative renal transplant recipients*  
Transplantation 1994; 58 (11): 1176-8
- 53 Plotkin SA, Starr SE, Friedman HM, Brayman K, Harris S, Jackson S, Tustin NB, Grossman R, Dafoe D, Barker C  
*Effect of Towne live virus vaccine on cytomegalovirus disease after renal transplant. A controlled trial*  
Ann Intern Med 1991; 114 (7): 525-31
- 54 Adler SP  
*Current prospects for immunization against cytomegalovirus disease*  
Infect Agents Dis 1996; 5: 29-35
- 55 Snyderman DR, Werner BG, Heinze-Lacey B, Berardi VP, Tilney NL, Kirkman RL, Milford EL, Cho SI, Bush HL, Levey AS, Strom TB, Carpenter CB, Levey RH, Harmon WE, Zimmerman CE  
*Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal transplant recipients*  
N Engl J Med 1987; 317: 1049-1054
- 56 Snyderman DR, Werner BG, Dougherty NN, Griffity J, Rubin RH, Dienstag JL  
*Cytomegalovirus immune globulin prophylaxis in liver transplantation*  
Ann Intern Med 1993; 119 (10): 985
- 57 Metselaar HJ, Rothbarth PH, Brouwer RML, Wenting GL, Jeekel J, Weimar W  
*Prevention of cytomegalovirus-related death by passive immunization: A double blind placebo controlled study in kidney transplant recipients treated for rejection*  
Transplantation 1989; 48: 264-266.
- 58 Hirsch MS, Schooley RT, Cosimi AB, et al  
*Effects of interferon-alpha on cytomegalovirus reactivation syndromes in renal-transplant recipients*  
N Engl J Med 1983; 308: 1489-1493
- 59 Cheeseman SH, Rubin RH, Stewart JA, et al  
*Controlled clinical trial of prophylactic human-leukocyte interferon in renal transplantation: effects on cytomegalovirus and herpes simplex virus infections*  
N Engl J Med 1979; 300: 1234-1249
- 60 Lui SF, Ali AA, Grundy JE, Fernando ON, Griffiths PD, Sweny P  
*Double-blind, placebo-controlled trial of human lymphoblastoid interferon prophylaxis of cytomegalovirus infection in renal transplant recipients*  
Nephrol Dial Transplant 1992; 7: 1230-1237
- 61 Balfour HH Jr, Chace BA, Stapleton JT, Simmons RI, Fryd DS  
*A randomised, placebo-controlled trial of oral Aciclovir for the prevention of cytomegalovirus disease in recipients of renal allografts*  
N Engl J Med 1989; 320 (21): 1381-1387
- 62 Green M, Reyes J, Nour B, Beatty D, Kaufman M, Wilson J, Todo S, Tzakis A  
*Randomized trial of ganciclovir followed by high-dose oral aciclovir vs ganciclovir alone in the prevention of cytomegalovirus disease in pediatric liver transplant recipients: preliminary analysis*  
Transplant Proc 1994; 26 (1): 173-174
- 63 Saliba F, Eyraud D, Samuel D, David MF, Arulnaden JL, Dussaix E, Mathieu D, Bismuth H  
*Randomized controlled trial of aciclovir for the prevention of cytomegalovirus infection and disease in liver transplant recipients*  
Transplant Proc 1993; 25 (1 Pt 2): 1444-1445
- 64 Frey DN, Matas AJ, Gillingham KJ, Canafax D, Payne WD, Dunn DL, Sutherland DE, Najarian JS  
*Sequential therapy - a prospective randomized trial of MALG versus OKT3 for prophylactic immunosuppression in cadaver renal allograft recipients*  
Transplantation 1992; 54 (1): 50-56
- 65 Nicol DL, MacDonald AS, Belitsky P, Lee S, Cohen AD, Butter-Suermann H, et al  
*Reduction by combination prophylactic therapy with CMV hyperimmune globulin and Aciclovir of the risk of primary CMV disease in renal transplant recipients*  
Transplantation 1993; 55 (4): 841-846

- 66 Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, Resta S, Dunn D, Gamberg P, Ratkovec RM, Richenbacher WE, Millar RC, DuMond C, DeAmond B, Sullivan V, Cheney T, Buhles W, Stinson EB *A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation* N Engl J Med 1992; 326 (18): 1182-1186
- 67 Rondeau E, Bourgeon B, Peraldi MN, Lang PH, Buisson C, Schulte KM, Weill B, Sraer JD *Effect of prophylactic ganciclovir on cytomegalovirus infection in renal transplant recipients* Nephrol Dial Transplant 1993; 3: 858-862
- 68 Hibberd PL, Tolkoff-Rubin NE, Conti D, Stuart F, Thistlethwaite JR, Neylan JF, Snyderman DR, Freeman R, Lorber MI, Rubin RH *Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial* Ann Intern Med 1995; 123 (1): 18-26
- 69 Winston DJ, Wirin D, Shaked A, Busuttill RW *Randomised comparison of ganciclovir and high-dose aciclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients* Lancet 1995; 346: 69-74
- 70 Brennan DC, Garlock KA, Singer GG, Schnitzler MA, Lippmann BJ, Buller RS, Gaudreault-Keener M, Lowell JA, Shenoy S, Howard TK, Storch GA *Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients* Transplantation 1997; 64 (12): 1843-1846
- 71 Flechner SM, Avery RK, Fisher R, Mastroianni BA, Papajcik DA, O'Malley KJ, Goormastic M, Goldfarb DA, Modlin CS, Novick AC *A randomized prospective controlled trial of oral aciclovir versus oral ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients* Transplantation 1998; 66 (12): 1682-1688
- 72 Rubin RH, Kemmerly SA, Conti D, Doran M, Murray BM, Neylan JF, Pappas C, Pitts D, Avery R, Pavlakis M, Del Busto R, Denofrio D, Blumberg EA, Schoenfeld DA, Donohue T, Fisher SA, Fishman JA *Prevention of primary cytomegalovirus disease in organ transplant recipient oral ganciclovir or oral aciclovir prophylaxis* Transpl Infect Dis 2000; 2 (3): 112-117
- 73 Yango A, Zanabli A, Morrissey P, Roy A, Gohh R *A comparative study of prophylactic oral ganciclovir and valganciclovir in high-risk kidney transplant recipients* J Am Soc Transp 2001; Abstract 202
- 74 Chou SW *Cytomegalovirus drug resistance and clinical implications* Transpl Infect Dis 2001; 3 Suppl 2: 20-24
- 75 Brown F, Banken L, Saywell K, Arum I *Pharmacokinetics of valganciclovir and ganciclovir following multiple oral dosages of valganciclovir in HIV- and CMV-seropositive volunteers* Clin Pharmacokinet 1999; 37 (2): 167-176
- 76 Pescovitz MD, Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, Heaton N, Woodruffe-Peacock C, Macey K, Tansley R *Valganciclovir for prevention of CMV disease: 12 month follow up of a randomized trial of 364 D+/R- transplant recipients* Am J Transpl 2003; 3 (Suppl 5): 299
- 77 Humar A, Paya C, Pescovitz MD, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, Heaton N, Woodruffe-Peacock C, Mueller B, Macey K, Tansley R *CMV virologic outcomes in D+/R- solid organ transplant recipients receiving valganciclovir vs ganciclovir prophylaxis* Am J Transpl 2003; 3 (Suppl 5): 430
- 78 Boivin G, Goyette N, Gilbert C, Pescovitz M, Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, Freeman R, Heaton N, Tansley R, Roberts N, Covington E *Valganciclovir prophylaxis is not associated with the emergence of cytomegalovirus UL97 and UL54 resistance mutations in solid organ transplant recipients: results from a multicenter trial* Am J Transpl 2003; 3 (Suppl 5): 431
- 79 Knox KK, Drobyski WR, Carrigan DR *Cytomegalovirus isolate resistant to Ganciclovir and Foscarnet from a marrow transplant patient (letter)* Lancet 1991; 337: 1292-1293
- 80 Boivin G, Erice A, Crane DD, Dunn DL, Balfour HH Jr *Ganciclovir susceptibilities of cytomegalovirus (CMV) isolates from solid organ transplant recipients with CMV viraemia after antiviral prophylaxis* J Infect Dis 1993; 168: 332-335
- 81 Slavin MA, Bindra RR, Gleaves CA, Pettinger MB, Bowden RA *Ganciclovir sensitivity of cytomegalovirus at diagnosis and during treatment of cytomegalovirus pneumonia in marrow transplant recipients* Antimicrob Agents Chemother 1993; 36 (6): 1360-1363
- 82 Jordan A, Borade SM, Lurain NS, Leischner J, Villanueva J, Vigneswaran WT, Garrity ER *Emergence of ganciclovir resistant cytomegalovirus in lung transplant recipients* Transplant 2001, Chicago, IL, May 11-16, 2001
- 83 Bowen EF, Emery VC, Wilson P, Johnson MA, Davey CC, Sabin CA, et al *CMV PCR viraemia in patients receiving ganciclovir maintenance therapy for retinitis: correlation with disease in other organs, progression of retinitis and appearance of resistance* AIDS 1998; 12: 605-611
- 84 Limaye AP, Corey L, Koelle DM, Davis CL, Boeckh M *Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants* Lancet 2000; 356 (9230): 645-610
- 85 Emery VC, Griffiths PD *Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy* Proc Natl Acad Sci USA 2000; 97: 8039-8044
- 86 Drew WL, Miner RC, Busch Dr, Follansbee SE, Gullett J, Mehalko SG, Gordon SM, Owen WF Jr, Matthews TR, Buhles WC, et al *Prevalence of resistance in patients receiving ganciclovir for serious cytomegalovirus infection* J Infect Dis 1991; 163 (4): 716-719
- 87 Jabs DA, Enger C, Dunn JP, Forman M *Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. CMV Retinitis and Viral Resistance Study Group.* J Infect Dis 1998; 177 (3): 770-773
- 88 Wolf DG, Yaniv I, Honigman A, Kassis I, Schonfeld T, Ashkenazi S *Early emergence of ganciclovir-resistant human cytomegalovirus strains in children with primary combined immunodeficiency* J Infect Dis 1998; 178 (2): 535-538
- 89 Olyaei AJ, Wahba IM, Norman DJ, Barry JM, Bennett WM, de Mattos AM *Incidence of CMV-disease beyond 90 days after ganciclovir prophylaxis: results from a cohort of high-risk renal transplant recipients* J Am Soc Nephrol 1999; 10: 763A
- 90 Emery VC, Cope AV, Bowen EF, Gor D, Griffiths PD *The dynamics of human cytomegalovirus replication in vivo* J.Exp Med 1999; 190: 177-182
- 91 Aitken C, Barrett-Muir W, Millar C, Templeton K, Thomas J, Sheridan F, Jeffries D, Yaqoob M, Breuer J *Use of molecular assays in diagnosis and monitoring of cytomegalovirus disease following renal transplantation* J Clin Microbiol 1999; 37 (9): 2804-2807
- 92 Imbert-Marcille BM, Cantarovich D, Ferre-Aubineau V, Richet B, Souillou JP, Billaudel S *Usefulness of DNA viral load quantification for cytomegalovirus disease monitoring in renal and pancreas/renal transplant recipients* Transplantation 1997; 63 (10): 1476-1481
- 93 Rautenberg P, Lubbert C, Weers W, Boetel E, Schweichler J, Zhou L, Costard-Jackie A, Kramer-Hansen H, Harder TC *Evaluation of the AmpliSensor PCR and the SHARP signal detection system for the early prediction of symptomatic CMV infection in solid transplant recipients* J Clin Virol 1999; 13 (1-2): 81-94
- 94 Abecassis MM, Koffron AJ, Kaplan B, Buckingham M, Muldoon JP, Cribbins AJ, Kaufman DB, Fryer JP, Stuart J, Stuart FP *The role of PCR in the diagnosis and management of CMV in solid organ recipients: what is the predictive value for the development of disease and should PCR be used to guide antiviral therapy?* Transplantation 1997; 63 (2): 275-279
- 95 Benedetti E, Mihalov M, Asolati M, Kirby J, Dunn T, Raofi V, Fontaine M, Pollak R *A prospective study of the predictive value of polymerase chain reaction assay for cytomegalovirus in asymptomatic kidney transplant recipients* Clin Transplant 1998; 12 (5): 391-395
- 96 Butt NM, Clark RE *High frequency of positive surveillance for cytomegalovirus (CMV) by PCR in allograft recipients at low risk of CMV* Bone Marrow Transplant 2001; 27 (6): 615-619
- 97 Singh N, Paterson DL, Gayowski T, Wagener M, Marino IR *Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus IV ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients* Transplantation 2000; 70: 717-722
- 98 Tinckam K, Djurdjev O, Stephens G, Ross P, Landsberg D *The efficacy of oral versus intravenously administered ganciclovir in the pre-emptive treatment of cytomegalovirus antigenemia in renal transplant recipients* Transplant 2001, Chicago, IL, May 11-16, 2001
- 99 Stocchi R, Szydlo R, Craddock C, Kanfer E, Apperley JF, Goldman JM, Ward KN *A comparison of prophylactic vs pre-emptive ganciclovir to prevent cytomegalovirus disease after T-depleted volunteer unrelated donor bone marrow transplantation* Bone Marrow Transplant 1999; 23 (7): 705-709
- 100 Kunzle N, Petignat C, Francioli P, Vogel G, Seydoux C, Corpataux J-M, Sahli R, Meylan PRA *Preemptive treatment approach to cytomegalovirus (CMV) infection in solid organ transplant patients: relationship between compliance with the guidelines and prevention of CMV morbidity* Transpl Infect Dis 2000; 2: 118-126
- 101 Paya CV, Wilson JA, Espy MJ, Sia IG, DeBernardi MJ, Smith TF, Patel R, Jenkins G, Harmsen WS, Vanness DJ, Weisner Rh *Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomised, placebo-controlled trial* J Infect Dis 2002; 185 (7): 854-860
- 102 Sagedal S, Nordal KP, Hartmann A, Midtvedt K, Foss A, Åsberg A, Degré M, Fauchald P, Rollag H *Pre-emptive therapy of CMV pp65 antigen positive renal transplant recipients with oral ganciclovir: a randomized, comparative study* Nephrol Dial Transplant 2003; 18: 1899-1908
- 103 Ketteler M, Kunter U, Floege J *An update on herpes virus infection in graft recipients* Nephrol Dial Transplant (2003); 18: 1708-1706
- 104 Hart GD, Paya CV *Prophylaxis for CMV should now replace pre-emptive therapy in solid organ transplantation* Rev Med Virol 2001; 11 (2): 73-81
- 105 Emery VC *Prophylaxis for CMV should not now replace pre-emptive therapy in solid organ transplantation* Rev Med Virol 2001; 11: 83-86
- 106 Crumpacker C, Marlowe S, Zhang JL, Abrams S, Watkins P and the Ganciclovir Bone Marrow Transplant Treatment Group *Treatment of cytomegalovirus pneumonia* Rev Infectious Dis 1988; 10 (suppl 3): 538-546

- 107 Dunn DL, Mayoral JL, Gillingham KJ, et al  
*Treatment of invasive cytomegalovirus disease in solid organ transplant patients with ganciclovir*  
Transplantation 1991; 51: 98
- 108 Dunn DL, Mayoral JL, Gillingham KJ, Loeffler CM, Brayman KL, Kramer MA, Erice A, Balfour HH Jr, Fletcher CV, Bolman RM 3rd, et al  
*Treatment of invasive cytomegalovirus disease in solid organ transplant patients with ganciclovir*  
Transplantation 1991; 51 (1): 98-106
- 109 Harbison MA, De Girolami PC, Jenkins RL, Hammer SM  
*Ganciclovir therapy of severe cytomegalovirus infections in solid-organ transplant recipients*  
Transplantation 1988; 46 (1): 82-88
- 110 de Koning J, van Dorp WT, van Es LA van 't Wout JW, van der Woude FJ  
*Ganciclovir effectively treats cytomegalovirus disease after solid-organ transplantation, even during rejection treatment*  
Nephrol Dial Transplant 1992; 7 (4): 350-356
- 111 Reed EC, Wolford JL, Kopecky KJ, Lilleby KE, Dandliker PS, Todaro JL, et al  
*Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo- controlled trial*  
Ann Intern Med 1990; 112: 505-510
- 112 Reed EC  
*Treatment of cytomegalovirus pneumonia in transplant patients*  
Transplant Proc 1991; 23 (suppl 1): 8-12
- 113 Emanuel D, Cunningham I, Jules-Elysee K, et al  
*Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of Ganciclovir and high dose intravenous immunoglobulin*  
Ann Intern Med 1988; 109: 777-782
- 114 Crumpacker C, Marlowe S, Zhang JL, Abrams S, Watkins P and the Ganciclovir Bone Marrow Transplant Treatment Group  
*Treatment of cytomegalovirus pneumonia*  
Rev Infectious Dis 1998; 10 (suppl 3): 538-546
- 115 George MJ, Snyderman DR, Werner BG, et al  
*Use of ganciclovir plus cytomegalovirus immune globuline to treat CMV pneumonia in orthotopic liver transplant recipients*  
The Boston Centre for Liver Transplantation  
Transplant Proc 1993; 25: 22
- 116 Wagner JA, Ross H, Hunt S, Gamberg P, Valentine H, Merrigan TD, Stinson EB  
*Prophylactic ganciclovir treatment reduces fungal as well as cytomegalovirus infections after heart transplantation*  
Transplantation 1995; 60 (12): 1473-1477
- 117 Falgas ME, Snyderman DR, Griffith J, et al  
*Clinical and epidemiological predictors of recurrent cytomegalovirus disease in orthotopic liver transplant recipients*  
Clin Infect Dis 1997; 25: 314
- 118 Van den Berg AP, Van Son WJ, Haagsma EB, et al  
*Prediction of recurrent cytomegalovirus disease after treatment with ganciclovir in solid-organ transplant recipients*  
Transplantation 1993; 55: 847
- 119 Gould FK, Freeman R, Taylor CE, et al  
*Prophylaxis and management of cytomegalovirus pneumonitis after lung transplantation: a review of experience in one center*  
J Heart Lung Transplant 1993; 12: 695
- 120 Kirklin JK, Naftel DC, Levine TB, et al  
*Cytomegalovirus after heart transplantation. Risk factors for infection and death: a multiinstitutional study*  
J Heart Lung Transplant 1994; 13: 394
- 121 Manez R, Kusne G, Green M, et al  
*Incidence and risk factors associated with the development of cytomegalovirus disease after intestinal transplantation*  
Transplantation 1995; 59: 1010
- 122 Sawyer MD, Mayoral JL, Gillingham KJ, et al  
*Treatment of recurrent cytomegalovirus disease in patients receiving solid organ transplants*  
Arch Surg 1993; 128: 165
- 123 Humar A, Uknis M, Carlone-Jambor C, Gruessner RW, Dunn DL, Matas A  
*Cytomegalovirus disease recurrence after ganciclovir treatment in kidney and kidney-pancreas transplant recipients*  
Transplantation 1999; 67 (1): 94-97
- 124 Sia IG, Wilson JA, Groettum CM, Espy MJ, Smith TF, Paya CV  
*Cytomegalovirus (CMV) DNA load predicts relapsing CMV infection after solid organ transplantation*  
J Infect Dis 2000; 181 (2): 717-720
- 125 Erice A  
*Resistance of human cytomegalovirus to antiviral drugs*  
Clin Microbiol Rev 1999; 12: 286-297
- 126 Rubin RH  
*Prevention and treatment of cytomegalovirus disease in heart transplant patients*  
J Heart Lung Transplant 2000; 19: 731-735
- 127 Rubin RH, Kemmerly SA, Conti D, Doran M, Murray BM, Neylan JF, Pappas C, Pitts D, Avery R, Pavlakis M, Del Busto R, DeNofrio D, Blumberg EA, Schoenfeld DA, Donohue T, Fisher SA, Fishman JA  
*Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral aciclovir prophylaxis*  
Transplant Infectious Diseases 2000; 2: 112-117
- 128 Speich R, van Der Bij W  
*Epidemiology and management of infections after lung transplantation*  
Clin Infect Dis 2001; 33 (suppl 1): S58-65
- 129 Wreghitt TG, Abel SJ, McNeil K, Parameshwar J, Stewart S, Cary N, Sharples L, Large S, Wallwork J  
*Intravenous ganciclovir prophylaxis for cytomegalovirus in heart, heart-lung, and lung transplant recipients*  
Transpl Int 1999; 12 (14): 254-260