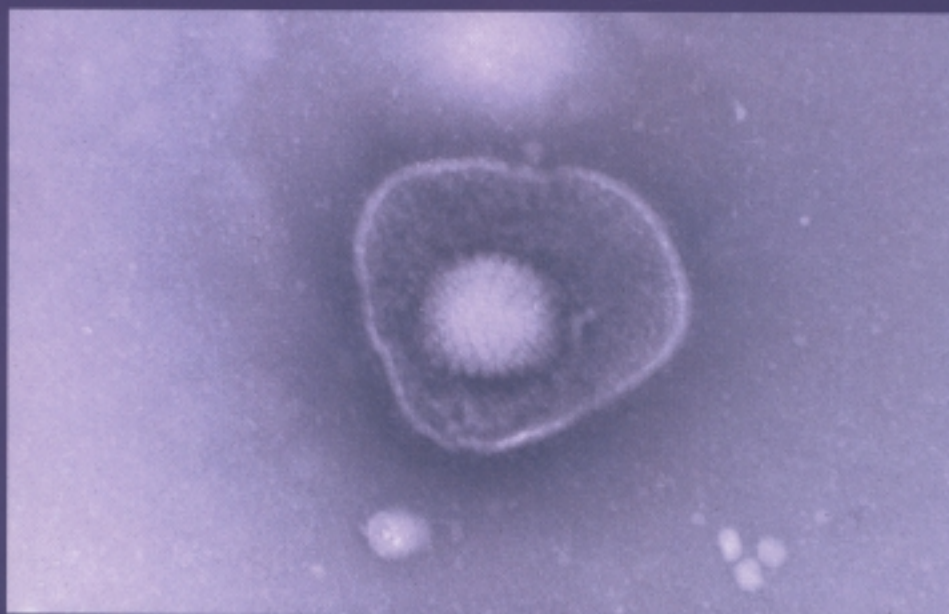


British Transplantation Society
Guidelines

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



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Published by the British Transplantation Society February 2002
ISBN 0 9542221 0 5

Contents

Recommendations	2	Prevention of CMV disease	14
For prophylaxis	2	CMV matching	14
For treatment	3	Vaccination	14
Need for guidelines	4	Passive immunoprophylaxis	14
Process of writing	5	Interferon	15
Biology of CMV in man	6	Anti-viral drug therapy	15
The diagnosis of CMV infection and disease	7	Acyclovir	15
Frequency of CMV and consequences of disease in immunosuppressed solid organ transplant recipients	9	Valaciclovir	15
Frequency of CMV in immunosuppressed solid organ transplant recipients	9	Ganciclovir	15
CMV and early allograft dysfunction	10	Pre-emptive anti viral prophylaxis	18
CMV and late graft rejection	11	Treatment of CMV disease	20
CMV and graft survival	12	Suggested audit standards	21
CMV and patient survival	13	Statements of potential conflicts of interest	22
		References	22

Recommendations

Evidence is presented using the principles adopted by the Canadian Task Force on the Periodic Health Examination [1]. 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 1 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 1 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 or where the donor and recipient are both sero-positive and the patient is treated with ATG/ALG/OKT3 should be offered prophylaxis against primary infection.

For renal transplant recipients

The recommended prophylactic strategy is either:

- a) Valacyclovir 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) High dose oral acyclovir for 12 weeks (Grade B)
- e) Intermittent intravenous CMV hyperimmune globulin for 12 weeks (Grade B)
- f) Serial measurements of viral load with treatment with intra-venous ganciclovir when levels predict disease (Grade B)

For liver transplant recipients

The recommended prophylactic strategy is either:

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

For kidney / pancreas transplant recipients

The recommended prophylactic strategy is either:

- a) Oral ganciclovir for ninety days post transplant (Grade C)
- b) Intra-venous ganciclovir for 28 days(Grade C)
- c) Valacyclovir for ninety days post transplant (Grade C)
- d) 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 either:

- 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) Valacyclovir for ninety days post transplant (Grade C)

For heart transplant recipients

The recommended prophylactic strategy is either:

- a) Oral ganciclovir for ninety days post transplant (Grade B)
- b) Intra-venous ganciclovir for 28 days (Grade B)
- c) Valacyclovir for ninety days post transplant (Grade C)
- d) 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 either:

- 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) Valacyclovir for ninety days post transplant (Grade C)

For heart transplant recipients:

No prophylaxis is recommended (Grade C)

For treatment

Patients with CMV disease should receive intra-venous ganciclovir for at least 14 days (Grade B)

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

Need for guidelines

CMV disease management post transplantation has been comprehensively reviewed by others [for example 2]. Guidelines were published in 1998 focusing on adult patients undergoing renal transplantation [3]. 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 [4]. Guidelines in development relating to solid organ transplant recipients are available on www.IHMF.org

There is a paucity of guidelines covering all solid organ transplant recipients. This area continues to undergo relatively rapid change. Most recently with the popularity of monitoring viral load and new drug therapies. This publication attempts to cover all solid organ transplant recipients and includes an up to date review of the literature.

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 Transplantation Society to prepare guidelines for the management of CMV disease after solid organ transplantation. The first draft was written by 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 suggestions from colleagues. Subsequently major revisions were made by Prof. PD. 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), Dr J.K. Parameshwar (Consultant Cardiologist Transplantation, Papworth Hospital, Papworth Everard, Cambridgeshire CB3 8RE) and Prof. P Griffiths.

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 mononuclear leukocytes and remains latent. Re-infection with a different human strain can occur, as can reactivation of the latent viral infection. Re-infection or reactivation usually result 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 [5].

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 [6, 7].

Transmission occurs from direct person to person contact. As the virus is labile intimate exposure to saliva, urine, breast milk, genital secretions, stools or blood has to occur and the risk of transmission to Health Care Workers is very low. Although congenital and peri-natal 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, particularly in developing countries. 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 re-activation cycle seen with herpes viruses this is not surprising. The detection of the classic large cells in culture takes several weeks and so is 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. In a group of liver transplant recipients, although the new assay was sensitive for CMV specific IgM, the IgM was detected before detection of virus only when the recipient was seropositive prior to transplantation. In this setting the assay had a very low positive predictive value [8].

For the detection of virus, direct 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 a problem as well as the fact that the test is positive in a proportion of patients with latent infection but no CMV disease [9]. CMV p65 antigen in circulating polymorphonuclear leucocytes in the buffy coat may discriminate between infection and disease, but again subjective interpretation and poorly reproducible results particularly if delay occurs in the processing of specimens are problems [10]. The rapid detection of CMV was first possible using the shell viral assay. Unfortunately a significant proportion of patients with viraemia are missed [11]. Tests based on the polymerase chain reaction carried out on plasma or whole blood as well as leucocytes are much more sensitive. In the early days of using this technique, contamination and inhibition were technical problems which had to be overcome, as well as the lack of standardisation between laboratories [12]. Experience has now allowed PCR diagnosis to be offered on a routine basis [13, 14] and the availability of commercial assays should facilitate wider introduction. Other methods such as hybrid capture for CMV DNA are also being evaluated. This assay should offer the advantages of objective CMV DNA detection and quantification without the technical hazards of PCR. In a recent study using two such commercial molecular assays the sensitivity for disease detection was 100% with disease predicted approximately twelve days before the onset of symptoms [6].

On occasions it is necessary to prove CMV organ specific dysfunction by

The Diagnosis of CMV Infection and Disease

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. As well as liver, native and allograft, bone marrow, lung, renal allograft as well as 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 an unlikely site [15].

Histopathology may be specific for CMV by identifying CMV inclusion bodies, or suggestive as in the detection of 'microabscesses' in the parenchyma in CMV hepatitis. Histopathology is insensitive compared to PCR [16]. The detection of CMV inclusions in an organ biopsied because of characteristic symptoms and signs meets the internationally agreed case definition of "CMV disease" [17]. 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 frequency 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 [18].

Primary infection with CMV typically occurs approximately four to six weeks post transplantation in a seronegative individual who receives an organ from a seropositive donor. The symptoms due to primary disease may occur as early as 20 days and are rare more than 50 days post transplantation [19]. 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 [20]. 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 is only available from relatively few publications. A 30% death rate in seronegative recipients of seropositive kidneys who received ALG has been reported in early literature. 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 charges and that effective antiviral prophylaxis was associated with an overall reduction in charges in the CMV sero-negative recipient CMV seropositive donor combination [21]. An audit from Manchester UK showed that 30% of renal recipients were high risk, of whom half experienced disease. On average eight days per at risk patient were spent in hospital managing CMV disease post transplant [22]. 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 and 7 out of 17 donor negative recipient positive patients developed CMV disease [8].

Because of the multiple human strains of CMV, even seropositive organ recipients are at risk of primary disease when receiving a graft from a seropositive donor with a different strain of virus [23].

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

In this situation the clinical syndrome is usually less severe than the consequences of primary infection in a seronegative recipient and disease onset is often delayed to approximately three months post-transplantation.

Seropositive recipients of seronegative grafts (and seronegative blood products) can develop CMV disease due to reactivation of latent virus. This is usually mild compared to primary infection and often delayed to approximately three months post-transplantation.

Leucodepleted or filtered whole blood has a very low risk for transmission of CMV disease [24].

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- γ . This may allow coincident infection with other viral or 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 [25]. Prophylaxis with valgancyclovir reduced biopsy-proven acute graft rejection by 50% in the D+R- subgroup [26] 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- γ by T-cells [27, 28] 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 [29, 30]. 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 which may indicate an increased humoral response to endothelial antigens which the authors postulate may be a risk factor for both vascular and chronic rejection [31].

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 suppresser 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 suggest this mechanism may have contributed to the relapse [29]. It has been known for

some while that in the rat aortic allograft model (of chronic vascular rejection) 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 [30]. In this model immunosuppression had a protective (rather than detrimental) effect on vascular wall histology [32]. In a whole organ model in the rat CMV significantly enhanced the development of chronic renal allograft rejection [33]. In other experiments, again in the rat allograft model, treatment with Ganciclovir blocked the early adventitial inflammation and reduced smooth muscle cell proliferation [34].

With this background there has been interest in a post-hoc analysis of a subset of a randomised placebo controlled study which reviewed 149 consecutive heart transplant patients who received either intravenous Ganciclovir or placebo for the initial 28 days after transplantation [35]. 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 versus control group. 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 emphasize, as it was not designed to address the specific question explored in this paper. Despite the intriguing animal in vivo and human data, there is other in

vitro work that shows that the induction of cell surface adhesion molecules after CMV infection is not influenced by Ganciclovir [36].

Sixty patients followed with at least four blood specimens for PCR analysis after liver transplantation showed CMV and human herpes virus 6 associated significantly with acute graft rejection [37]. In a complex paper 242 consecutive renal transplants were prospectively followed [38]. One-hundred and fifty seven experienced CMV infection, 85 did not. Eighty-five of the infected patients were randomly paired with non-infected patients and the non-infected patients given a date for a fictitious CMV infection shared with the real infection in that pair. The incidence of acute rejection after CMV infection was higher among those infected, 45% versus 11% in the non-infected.

Cytomegalovirus and late graft rejection

The large multicenter study of oral ganciclovir prophylaxis in liver transplant recipients in the first year showed no difference in chronic rejection, although this result is felt by many authorities to be because of the short length of follow up [19]. 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 obstruction compared with 72% of the CMV patients [39]. In 128 heart transplant recipients who were transplanted between 1992

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

and 1993, all of whom received four weeks of intravenous Ganciclovir and then acyclovir 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 or asymptomatic CMV on the subsequent development of allograft vasculopathy [40]. This area of the potential impact of acute CMV disease on chronic vascular rejection will need addressing 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 donor positive compared to when the donor was seronegative was of the order of 4% at three years [41]. Some single centres have reported even more deleterious outcome [42], but others have shown no such effects [43].

Cytomegalovirus and graft survival

In a single centre report of 1339 renal transplant recipients an attempt was made to separate out the impact of acute rejection and CMV disease on long term graft survival. A multivariate analysis showed that CMV disease appeared to influence long term graft survival but only if the individual had also experienced acute rejection [44].

In a liver transplant population of 33 patients who received 57 transplants persistent CMV infection, as defined by serial PCR measurements, was statistically significantly associated with graft loss from chronic rejection. But in this series there was no significant effect of, for example, donor positive recipient negative, or symptomatic CMV disease on chronic rejection, perhaps as a consequence of small sample size [45]. The data in this solid organ group is equivocal. In the pre-antiviral era, there was strong evidence linking CMV to chronic rejection [46] and there are two other studies linking persistence of CMV in the liver to the development of chronic rejection [47, 48].

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 of those who were transplanted before Ganciclovir was available and those transplanted afterwards. In the early group the survival of the recipient negative donor positive patients was significantly poorer [49]. However, close inspection of the survival curves show no change in late graft survival before and after the use of universal prophylaxis, arguing against a role for CMV infection causing late graft vasculopathy in renal transplantation.

Cytomegalovirus and patient survival

Prophylaxis protects in the high risk donor CMV positive/recipient CMV negative group from early death 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 [50].

Prevention of CMV disease

Because of the frequency of this iatrogenic complication of solid organ transplantation and the associated morbidity and mortality there has been considerable interest in developing an effective prophylactic strategy.

CMV matching

CMV matching to avoid transplanting a seronegative individual with a seropositive organ is an option. Given the lifesustaining nature of successful heart, lung and liver transplantation it is very rarely practised 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. 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 seronegative patients failed to produce antibodies. In those transplanted in the placebo group 71% developed disease compared with 56% in the vaccinated cohort [51]. There have been other studies when the rate

of CMV disease was decreased from approximately 50% to 37% and severe disease from 29% to 5% in the vaccinated patients [52, 53].

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 [54].

Passive immunoprophylaxis

This has been explored in solid organ transplantation in a number of randomised trials [55, 56, 57]. However only one, in liver transplant recipients was placebo controlled [56]. This study randomised 141 patients, a third of whom received OKT3. The hyperimmune globulin provided significant overall protection from severe disease. However, no protection in the recipient negative/donor seropositive sub-group was seen. These studies are difficult to interpret because of different proportions of high risk patients in each study group and different definitions of CMV disease. However, if the rate of CMV disease as defined in each paper in the untreated group is compared with that seen in the treated group then the results can be summarized to demonstrate that intravenous immunoglobulin reduces 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) but 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 [58, 59]. In a formal blinded placebo controlled study in renal transplant recipients a similar result was obtained [60].

Anti-viral drug therapy

Acyclovir

Acyclovir 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 each arm [61]. In liver transplantation results have been contradictory with some or no benefit seen [62, 63]. Others have shown no benefit in renal transplantation if ATG/ OKT3 was used [64]. Acyclovir may only provide significant protection in less high risk recipients such as seropositive recipients of seropositive organs or where the degree of initial immunosuppression is relatively modest, for example in that small percentage of renal recipients who receive Cyclosporin A monotherapy.

Another strategy is to use CMV hyperimmune globulin in combination with antiviral drugs, this has been done in an uncontrolled study and it is difficult to assess the utility of this approach [65].

Valaciclovir

This prodrug has a three to five fold improved oral bioavailability compared to Acyclovir. Valacyclovir has recently been studied in a randomised prospective placebo controlled study in a renal transplant cohort of 208 donor positive recipient negative and 408 recipient positive patients [26]. In the high risk donor positive recipient negative group the incidence of CMV disease at 90 days was 45% in the placebo and 3% among those who received Valacyclovir. Among the recipient positive patients, however, there was still a significant difference but at the low incidences of at 6% and 0%. At six months the incidence of CMV disease had increased to 45% among seronegative recipients of the placebo and to 16% in the seronegative recipients of Valacyclovir. There was also a highly significant difference in the frequency of biopsy confirmed acute rejection with the Valacyclovir group experiencing 26% and the placebo group 52% in the donor positive recipient negative group by six months.

Ganciclovir

A variety of regimens using relative short courses of intravenous Ganciclovir have been used [66, 67]. Intravenous Ganciclovir reduced the frequency of CMV disease to a quarter of that seen in the control group in a randomised blinded outcome study [68]. In a randomised comparison of intravenous ganciclovir for 100 days and acyclovir initially intravenous and then high dose oral for 100 days in liver transplant recipients symptomatic CMV disease occurred in 0.8% of the ganciclovir and 10% of the aciclovir groups (p=0.002)

Prevention of CMV disease

[69]. In contrast, where the degree of immunosuppression is more intense, as is typical in cardiac transplantation, intravenous Ganciclovir for 28 days was shown in a placebo controlled randomised controlled trial to have no impact on the highest risk (donor positive/recipient negative) sub-group [66]. In this situation other strategies, such as longer courses, the combination of antiviral drugs and CMV hyperimmune globulin or more protracted intravenous or oral drug therapy should be evaluated.

Despite its poor bioavailability a prospective double blind placebo-controlled randomised clinical trial of oral ganciclovir in liver transplant recipients (only excluding donor and recipient seronegative) 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% ($p < 0.001$) [19]. These findings are consistent with a similar study from a renal transplant group where 42 patients were followed for six months, randomised to receive either Ganciclovir or Acyclovir. Again all except donor and recipient seronegative were included and all patients bar one received quadruple induction therapy including ALG [70].

One hundred and fifty five donor positive and recipient negative recipients of a variety of solid organs all received five to ten days of intra-venous ganciclovir and then either oral ganciclovir or acyclovir for a further 12 weeks. Approximately one quarter were 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 acyclovir and 3 out of 77 in the ganciclovir group [71]. In a randomised prospective controlled trial of oral Acyclovir versus oral Ganciclovir in a renal transplant group who received quadruple immunosuppression including OKT3 in the donor positive recipient negative group CMV disease occurred in 5 out of 13 in the Acyclovir group and 0 out of 14 in the Ganciclovir group during the period of prophylaxis. However, post-prophylaxis three patients in the Ganciclovir group had evidence of infection [72].

A retrospective study compared 60 renal transplant recipients who had received oral Ganciclovir with 70 who had received Valacyclovir. There was no difference in incidence of CMV infection in the two groups, 6.9% versus 5.4% [73].

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. Valganciclovir, which offers with oral therapy a ten fold increase in plasma ganciclovir levels to that achieved with the oral formulation of Ganciclovir, may represent a significant advance for both treatment and prophylaxis [74] although similar side effects are expected.

With all prophylactic strategies there are disadvantages. To be effective they rely to a more or less degree on good patient compliance. The treatments add to the cost of the procedure and are likely

to be 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 [75, 76, 77, 78], may reflect difficulties with cell culture assays [79]. When PCR was used, 22% of 45 AIDS patients receiving long term GCV developed resistance [80] and a figure of 20% has recently been reported for solid organ transplant recipients [81]. The duration of therapy is likely to be important. [79]. Ganciclovir resistance is shown in about 8% of patients with AIDS after three months' treatment [82] rising to 11 % with resistant blood or urine CMV isolates at six months, and 28% at nine months [83] . The severity 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 three weeks after starting Ganciclovir [84]. 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) the rate of CMV disease in those receiving prophylaxis and those not was strikingly different at three months but was the same by the time both the groups had reached one year [85].

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 are regularly surveyed and when judged to be at high risk of developing CMV disease are treated, 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 and antigenaemia. Results should be interpreted in terms of the rapid dynamics of CMV replication [14, 86]. These have sensitivities which vary from 57% to approximately 85% and a specificity from about 35% to 90%. A publication which showed the plot of probability of CMV disease against viral load in a renal transplant population is instructive [87]. At a viral load of 5 log₁₀ 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 [88] and other solid organ recipients [89, 90].

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 would treat a large fraction of patients who did not necessarily require it. The authors noted that none of the 29 patients who were continuously negative for CMV PCR developed CMV

disease, which is reassuring. However, as a guide to treatment in this setting it seems somewhat limited [91]. In a British bone marrow transplant unit 7 of 10 CMV positive recipients of a CMV positive graft developed CMV DNAemia with only 3 going 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 aetiology of the positive tests in these cases is unclear and again emphasizes that there is significant laboratory variation in expertise in this area [92].

Several authors have reported on a prophylactic strategy that follows at risk patients with serial measures of CMV antigenemia and then treated with intravenous ganciclovir patients who are predicted to be about to develop CMV disease. 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) [93]. In a study of renal transplant recipients who were sero positive at the time of transplantation two different strategies were adopted. 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 [94]

In 49 patients who received unrelated donor bone marrow transplants who 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% verses 30% in the pre-emptive verses prophylactic Ganciclovir group $p=0.07$ [95].

In one report [96] a retrospective study of 39 renal, 28 liver and 23 heart transplant recipients experienced 26 episodes of infection managed according to the pre-emptive strategy, 4 of whom developed CMV disease and there were no deaths. 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 that if a pre-emptive strategy is put in place then it is most important that all the elements for monitoring it appropriately are available.

In a recent review [97] the authors, when discussing prophylaxis for CMV and solid organ transplantation) point out that "conventional prophylactic therapy has a large body of supportive controlled clinical studies demonstrating efficacy and

cost-effectiveness. 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 preemptive 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 [98]. These include preventing antigen presentation to the immune system so that patients develop disease once the drug is stopped and the development of resistance. Clearly, the choice between prophylaxis and pre-emptive therapy 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 specific antiviral therapy [99, 100]. The former option is easier for renal rather than life-sustaining transplants. Intravenous ganciclovir has made a major impact on the mortality and morbidity seen from this condition [100, 101, 102, 103] although the only randomised placebo controlled trial, in bone marrow transplant patients with CMV gastroenteritis did not show clinical benefit [104]. In the situation where there is fever and a white blood count greater 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 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 due to CMV disease can be treated by ganciclovir. This approach to treatment is in line with that recommended by others [105, 106, 107]. Very high doses of intravenous hyperimmune globulin (0.5 g/kg body weight) have been used for treatment of pneumonitis in conjunction with intravenous ganciclovir [108].

A common clinical problem is deciding on the duration of intravenous treatment after resolution of clinical signs. 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 another infection as well as CMV disease should always be ruled out by repeated clinical examination and special investigations. In one sub-group analysis of a randomised controlled trial of intravenous Ganciclovir in cardiac transplant recipients was shown to decrease the incidence of fungal infections [109].

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 [110, 111, 112, 113, 114, 115]. In one study on kidney and kidney/pancreas recipients relapse was seen in approximately one third of patients after treatment of the initial episode with Ganciclovir [116]. The qualitative measurement of CMV viral load may allow the risk of relapse to be predicted [117].

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 [118, 119].

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, GI 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 [3, 26].

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 [19, 69].

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 [120].

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 [2, 3, 26, 121, 123].

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 [66, 123].

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 [2, 3, 26, 121, 123].

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 principally from Fujisawa, Novartis and Roche. He has received honoraria for contribution to Advisory Boards for both Roche and Wyeth. Research of collaborators has been in part sponsored by the above named companies as well as eight different Foundations

Dr. J. OGrady 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.

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.

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