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# Management of human cytomegalovirus infection and disease after allogeneic bone marrow transplantation

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ABSTRACT

*Background and Objective.* Human cytomegalovirus (HCMV) infection and disease remain a major cause of morbidity and mortality after bone marrow transplantation. HCMV disease, especially pneumonitis, may be treated with ganciclovir and immunoglobulin but even so the outcome is poor with mortality rates of 30-70%. It is therefore imperative to treat HCMV infection before it develops into disease. The aim of this article is to describe the main strategies used to prevent HCMV infection and to improve the survival after CMV disease in bone marrow transplant recipients.

*Information sources.* In the present review, we examined personal papers in this field and articles published in journals covered by the Science Citation Index and Medline.

*State of the Art.* Major advances have been made in preventing HCMV infection and disease through two different approaches, both of which reduce HCMV induced morbidity and mortality: in pre-emptive therapy, patients are given ganciclovir when HCMV infection is first identified and this is continued 3-4 months after transplantation; in prophylactic therapy ganciclovir is given to all patients at risk of HCMV disease from engraftment up to 3-4 months post transplantation. Each strategy has advantages and disadvantages and there is no evidence for the superiority of one over the other since the overall survival is the same and the incidence of death from HCMV disease is similar.

*Perspectives.* The use of more sensitive tests such as HCMV PCR or antigenemia may improve the outcome but probably will not eradicate all HCMV disease. Future possible strategies could include adoptive transfer of $CD8^+$ HCMV-specific cytotoxic T lymphocytes clones derived from the donor marrow or boosting donor or patient immunity using subunit anti-HCMV vaccines such as gB or pp65.


Key words: CMV infection and disease, allogeneic BMT

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## Human cytomegalovirus infection and disease

Human cytomegalovirus (HCMV) is a ubiquitous herpesvirus that infects 40-100% of adults. Primary infection with HCMV always leads to the virus persisting for long periods in the host as a latent infection. In immunocompromised individuals HCMV can reactivate (HCMV infection) and may give rise to a clinical illness (HCMV disease).[1] Several studies show that bone marrow progenitors act as a reservoir of HCMV and transmit the viral genome to peripheral blood monocytes, without lytic-gene expression, until they leave the circulation and undergo tissue-specific differentiation to macrophages.[2-6]

Infection and disease due to HCMV are major complications of allogeneic bone marrow transplantations (BMT)[7] and in several studies in the 1980s the incidence in seropositive patients have been reported as 42% to 69% and 16% to 25%, respectively.[1,8-9] HCMV infection commonly occurs one to three months after transplant and may be followed by disease manifestations approximately 15 days later.[10] Pneumonia remains the most frequent manifestation of HCMV disease with an incidence of about 15% and a mortality rate between 30-52%.[11,12] The clinical presentation includes fever, non productive cough, tachypnea, hypoxemia and bilateral interstitial infiltrates.[7,13,14] HCMV can also be a less frequent cause of gastrointestinal ulcers (affecting the entire gastrointestinal tract),[15,16] and retinitis.[17] Syndromes that have also been associated with HCMV include a mononucleosis-like illness (fever, arthralgia, malaise), marrow suppression, and hepatitis.[18-21]

## Risk factors for HCMV infection and disease in allogeneic BMT

The major risk factor for HCMV infection is the serostatus of the patient prior to transplant.[7] HCMV seropositive recipients, regardless of their donors' antibody status, are at high risk of recurrent HCMV infection, whereas HCMV seronegative individuals who receive marrow from HCMV seropositive donors are at a lower risk of primary infection[7,22] suggesting that the donor marrow is of limited impor-

tance in the transmission of HCMV. Those at lowest risk are HCMV-seronegative patients with a seronegative donor since the main risk factor for HCMV infection is the use of blood products from seropositive donors (Table 1).[23,24] The risk of HCMV disease is primarily dependent on the risk of HCMV infection, and HCMV viremia in particular has a high positive predictive value for subsequent disease.[10] Secondary factors include severe graft-versus-host disease (GvHD),[25] a transplant from a volunteer unrelated donor (VUD)[26] and delayed reconstitution of the HCMV-specific cytotoxic T cell response.[27]

## HCMV infection and disease in VUD BMT recipients

Allogeneic BMT is a widely accepted treatment for hematologic malignancies, bone marrow failure syndromes and congenital disorders of the lymphohemopoietic system.[28] The probability of having an HLA-identical sibling donor is about 25% so to increase the availability of donors, transplants from unrelated donors have been performed.[29-30] The use of VUDs is associated with increased morbidity and mortality when compared with HLA-identical sibling donor BMT, due to increased rates of GvHD, graft failure and infections especially from HCMV.[26,31-35] The reasons for this increased risk of HCMV infection are multifactorial and include delayed immune recovery, and an increased risk of severe GvHD.[26,36-39]

As already reported elsewhere,[36,40] T cells play an important role in controlling HCMV infection and disease. HCMV-specific $CD8^+$ T cells were shown to be protective in humans.[41] Reconstitution of $CD8^+$ T cells specific for HCMV was reported to correlate with prior or concurrent recovery of $CD4^+$ HCMV-specific Th responses.[42] Some authors[43,44] found a correlation between the lack of Th cell proliferation capacity and the occurrence of HCMV pneumonia after BMT. In fact, the lack of recovery or a progressive decline of $CD4^+$ T cells appear to be negative prognostic factors for patients with HCMV infection.

In VUD-BMT recipients, antiviral therapy, in particular with ganciclovir (GCV), is started early after transplant and may be responsible for the delay in immunologic recovery against HCMV and consequently for late HCMV infection and disease when the antiviral drug is discontinued.

Antiviral therapy may contribute to the delay in recovery of HCMV-specific T-cell responses by several mechanisms. GCV inhibits mitogen- and antigen-induced T-cell proliferation *in vitro* because of effects on cellular DNA synthesis.[45] It exerts its antiviral effects at the stage of viral DNA replication; therefore, in the presence of the drug, infected cells may express immediate early (IE) and early (E) gene products, but not the full repertoire of HCMV genes necessary for replication and new virion formation.[46] In latently infected HCMV seropositive individuals, the class I HLA restricted $CD8^+$ cytotoxic T-cell (CTL) response to HCMV is predominantly specific for epitopes derived from structural virion proteins and these antigens are presented rapidly after entry of virions into the cytoplasm.[47] Thus, in individuals receiving GCV, the viral antigens available may not be adequate to activate host T-cell responses resulting in the failure to reconstitute CMV-specific $CD4^+$ Th and $CD8^+$ CTL, or responses specific for IE or E viral gene products may be preferentially activated and these CTL may not be sufficient to provide protective immunity.

Moreover, growth of CTL is impaired in patients who develop severe GvHD[27] and VUD-BMT patients usually have an increased incidence of GvHD compared to sibling transplant recipients. However, increased incidences of HCMV infection and disease are observed in VUD BMT patients even in the absence of GvHD.[48] The reason for this may be that GvHD prophylaxis and treatment are in themselves immunosuppressive and increase the incidence of HCMV disease.[7,10,12,49] *In vivo* and *in vitro* studies have revealed that alloantigenic stimulation of blood cells from healthy donors facilitates the reactivation of HCMV.[4,50-52] Genetic disparity is greater in VUD BMT recipients than in genotypically HLA-identical sibling donors,[53-55] so alloantigen stimulation by unknown or undefined histocompatibility antigens may be another important factor affecting the incidence of HCMV infection and disease in VUD BMT.

## Antiviral agents with activity against HCMV

Acyclovir was the first antiviral agent with *in vitro* activity against HCMV used for treating HCMV disease, unfortunately without success.[56] GCV (9-1,3 dihydroxy-2propoxymethyl guanine),[57] an acyclic nucleoside structurally related to acyclovir, has a marked antiviral effect in HCMV-infected lung tissue[58] and in combination with intravenous immune globulin (IV IG) is the current treatment of choice for HCMV disease.[12,48,59-61] Foscarnet (trisodium phosphonoformate) inhibits herpesvirus DNA polymerase activity and has been shown to suppress replication

*Table 1. Risk of HCMV disease after allogeneic BMT.*

| HCMV antibodies | | Risk of HCMV disease | |
|---|---|---|---|
| Donor | Recipient | Sibling donor | Unrelated donor |
| - | - | Very low (23-24) | Very low (23-24) |
| + | – | Moderate (7, 22) | Moderate (7,22) |
| – | + | High (7,22) | Very high (7, 22) |
| + | + | High (7, 22) | Very high (7,22) |

*HCMV: human cytomegalovirus.*

of HCMV *in vitro*.[62-63] Several reports describe, with various results, the use of foscarnet (alone[64-68] or in combination with GCV[69]) to treat CMV disease in allogeneic BMT. In spite of these therapeutic options, treatment of HCMV disease is frequently unsuccessful. In fact, HCMV sometimes becomes resistant to treatment,[70-71] whilst in other situations antiviral drugs have to be discontinued due to intolerance or occurrence of severe side effects (myelosuppression for GCV and renal failure for foscarnet). Given the poor outcome of CMV disease and pneumonitis in particular, effective prophylaxis is essential.

## Diagnostic techniques for HCMV detection

In the management of patients at risk of HCMV disease, it is important to have rapid and sensitive methods of HCMV detection. Early diagnosis of HCMV infection after allogeneic bone marrow transplantation can be performed in 3 different ways: immunocytochemistry of infected human fibroblasts, the DEAFF (detection of early antigen fluorescent foci);[72] the expression of the 65 kDa lower matrix phosphoprotein (pp65) in peripheral blood leukocytes, so called HCMV antigenemia;[73-74] polymerase chain reaction (PCR) for amplification of viral nucleic acid sequences.[75-76] The DEAFF is not sensitive enough to identify all infected patients prior to the onset of disease because a substantial number of patients develop HCMV disease without preceding viremia, as defined by this test;[77] in addition, it appears to be of limited value in monitoring antiviral treatment or prophylaxis because the patients become negative within 2-3 weeks after initiation of treatment regardless of clinical outcome.[77]

Recent studies have compared HCMV-PCR and HCMV antigenemia[78] and both tests are highly sensitive in the diagnosis of HCMV infection (>85% sensitivity); HCMV antigenemia appears to reflect the viral load in the systemic circulation.[78,79] In the setting of allogeneic BMT, it is a sensitive, specific and rapid technique which detects infection earlier than the DEAFF test.[80] HCMV antigenemia is also important for the prediction of subsequent HCMV disease because antigenemia can be detected from 1 to 4 weeks before the onset of clinical manifestations of HCMV infection.[81,82] The level of HCMV antigenemia is reported to be inversely correlated to host immunocompetence.[83,84] On this subject, Takenaka *et al*.[34] report that the peak levels of HCMV antigenemia are increased in VUD BMT patients and that in these patients the HCMV antigen-positive cells do not disappear as rapidly after GCV treatment as they do in HLA-identical sibling donor transplant patients. These results suggest that host immunocompetence may be profoundly suppressed in VUD BMT patients. Similarly, the incidence of HCMV infection and HCMV antigenemia in patients who receive a transplant from a VUD are also higher than in those who receive transplants from one locus HLA-mismatched related donors, suggesting that there may be a difference in the degree of alloantigenic stimulation between these two groups.[34] Testing of HCMV-DNA by PCR can be carried out on a variety of clinical specimens including peripheral blood leukocytes (PBL), plasma, serum, bronchoalveolar lavage fluids, tissue, and urine. Variations of the technical aspects of the PCR assay, the use of DNA versus RNA, as well as the type of clinical material tested may alter the sensitivity of the assay. In BMT patients, detection of HCMV-DNA in PBL is the earliest indicator of HCMV reactivation and persists longer than both DEAFF and antigenemia after institution of antiviral treatment.[79,84,85] Recent studies have confirmed these results using plasma-PCR or PCR of bronchoalveolar lavage.[86,87] However, HCMV-DNA can be detected in a substantial number of patients not at risk of HCMV disease[79,88] so that it would be necessary to distinguish the latent from the active state of transcription of the viral genes, perhaps by using quantitative PCR.

In this regard, Gerna *et al.*[89] showed that quantification of HCMV DNA in peripheral blood leukocytes (PBL) could be an excellent tool for monitoring HCMV infections and antiviral treatment in BMT recipients, producing much better information than qualitative PCR. They retrospectively quantified HCMV DNA levels by PCR in pediatric BMT recipients, most of whom had been given pre-emptive therapy on the basis of antigenemia values > 2 and found that: starting therapy in the presence of a mean antigenemia level of 9.3 (range 1-22) corresponding to a mean DNA level of 184.6 (range 20-710) genome equivalents (GE) avoided occurrence of any major HCMV-related clinical complications; clinical symptoms were associated with antigenemia levels > 100 and DNA levels > 1000 GE; the effect of antiviral treatment could be more carefully monitored by quantification of viral DNA.

## Prevention of HCMV disease after allogeneic BMT (Table 2)

### *Use of IV IG*

Use of IV IG or hyperimmune globulin remains a controversial issue and in both HCMV seronegative and seropositive recipients the main benefit is probably non-specific and due to a reduction in the incidence of both GvHD and bacterial infection.[48,90]

### *Prevention of HCMV infection and disease in HCMV seronegative patients*

The use of HCMV seronegative blood products[24,91] or leukocyte-depleted platelets and HCMV seronegative red blood cells[92] can prevent HCMV infection in HCMV seronegative recipients who receive marrow from a seronegative donor. Moreover, recent technical advances mean that leukocyte depletion of red blood cells is now possible and this may obviate the need for HCMV antibody screening. Bowden *et al*.[92]

*Table 2. Strategies for prevention of HCMV disease in allogeneic BMT patients.*

| *HCMV antibodies* | *Strategy* | *Results* |
|---|---|---|
| Recipient/donor seronegative | HCMV seronegative blood products | Very effective[24, 91-92] |
| Recipient seronegative. Donor seropositive | HCMV seronegative blood products | Ineffective[24, 91] |
| | Intravenous immunoglobulins | Questionable[48, 90] |
| | Antiviral drugs | Little data. Presume effective as below |
| Recipient seropositive | Intravenous immunoglobulins | Questionable[48, 90] |
| | Acyclovir prophylaxis | Partially effective[19, 93] |
| | Foscarnet prophylaxis or pre-emptive therapy | Effective but not fully assessed[100-105] |
| | Ganciclovir prophylaxis or pre-emptive therapy | Effective but toxic[18, 76-77, 94-99] |

showed, in a prospective randomized trial, that filtration of blood products is as effective as HCMV-seronegative blood products in preventing transfusion acquired HCMV infection after transplantation in HCMV-seronegative recipients with HCMV-seronegative donors. They found that the two methods are equivalent for prevention of HCMV infection despite exposure to blood products from a very large number of different donors.

Unfortunately, this policy does not reduce the rate of primary HCMV infection in seronegative individuals who receive marrow from a seropositive donor.[24,91] The use of prophylactic antiviral therapy in this group of patients is difficult to justify as the majority will not develop HCMV infection or disease. In these cases strategies using the antigenemia[73,74] or PCR assays[75,76] may be the best way to identify patients at higher risk of HCMV disease.

### *Prevention of HCMV infection and disease in HCMV seropositive patients*

Effective prophylaxis for HCMV infection and disease in patients who are HCMV seropositive at the time of transplantation has not been clearly established. In these patients the main strategy is to start appropriate antiviral drug therapy to control HCMV infection before HCMV disease has developed. Unfortunately, none of the published studies were designed to take account of possible differences in response between sibling and VUD BMT patients. Such differences are likely to be important in view of the increased risk of chronic GvHD and infections in the latter group.[26]

The first preventive antiviral drug strategy to be devised involved acyclovir; in a non-randomized prospective study acyclovir was observed to delay HCMV infection and reduce HCMV disease if given at a high dose (500 mg/m$^2$) starting 5 days before BMT and continuing until day 30 after the transplant.[93] A subsequent double-blind placebo controlled trial was undertaken by the *European Acyclovir Study Group* in which patients were given either high-dose intravenous or oral acyclovir for the first 30 days after transplantation.[19] Those given intravenous acyclovir subsequently received oral acyclovir or placebo until day 210. The patients who received long-term acyclovir therapy showed a delay in the mean time of HCMV infection to 57 days after transplantation and a 19% survival advantage at one year after BMT. The results of this study have been questioned, with reference to differences in treatment of HCMV disease at different centres, and have been, moreover, superseded by the availability of more potent anti-HCMV drugs, ie GCV and foscarnet.

There are currently two different approaches to the prevention of HCMV disease, and hence a reduction in the associated rates of morbidity and mortality. The first approach is to use antiviral therapy *pre-emptively*. The majority of the published studies have adopted GCV as the antiviral agent. Active HCMV replication (HCMV infection) during the first 3-4 months after BMT (defined as the presence of HCMV in blood, urine, pharyngeal washings or bronchoalveolar lavage fluid), was used to identify those patients at highest risk of HCMV disease. These patients were given pre-emptive treatment with GCV which continued until 3-4 months after transplantation. Two large studies[77,94] showed a significant reduction in HCMV morbidity and mortality but the policy failed in some cases because HCMV disease coincided with the first detection of HCMV infection. Moreover, GCV therapy caused neutropenia at a median of 35 days treatment.[77] One study[77] demonstrated an improvement in survival whereas there was no change in outcome in the other.[94] The explanation probably lies in differences between the two studies (eg. total GCV dose, patient selection).

In the second approach GCV is used prophylactically. Thus, all patients at risk of HCMV disease as defined by pre-transplant seropositivity are given prophylaxis as soon as engraftment occurs and this is continued for 3-4 months after BMT. The intention is to prevent CMV infection completely thus eliminating the possibility of concurrent HCMV infection and disease. The dose of GCV used varied from 5-6 mg/kg/day and the frequency of dosing from 3 times

weekly to daily; such differences may well have influenced the likelihood of breakthrough HCMV infection. In the three early studies[95-97] which evaluated GCV prophylaxis, a historical control group was used for comparison of rates of HCMV disease. The results in each case were similar showing a decrease in the incidence of HCMV infection but no improvement in overall survival. Subsequently, two double-blind placebo controlled trials[18,98] clearly demonstrated that prophylaxis is very effective at reducing the incidence and severity of HCMV infections in these patients but confirmed that there was no improvement in overall survival. Moreover, as in the studies using pre-emptive therapy, prolonged use of GCV induced neutropenia[18,98] and increased the risk of bacterial and fungal infection.[98] Furthermore, many patients were exposed to the toxic side effects of antiviral therapy although they would never have developed HCMV infection or HCMV disease.[35] Finally, patients given prolonged GCV therapy are not able to reconstitute the immune response to HCMV fully and are thus at risk of late HCMV disease after therapy has been discontinued.[27]

Therefore, although prophylactic and pre-emptive GCV[18,77,94,98] are effective at reducing HCMV disease, the results are not uniformly successful. Recent studies have therefore been aimed at better identification of the subgroup of patients at highest risk of HCMV disease and at using short courses of GCV as opposed to prolonged therapy in order to reduce toxicity. This has been made possible by the development of antigenemia and PCR assays. Thus, whereas the GCV studies described above[18,77,94,98] used the DEAFF test[72] for rapid diagnosis of HCMV infection, more recent investigations have used more sensitive tests (antigenemia[73,74] and PCR assays[75,76]) that allow detection of HCMV infection earlier than the DEAFF and hence give earlier warning of HCMV disease.

Einsele *et al*.[76] compared pre-emptive GCV based on HCMV infection as detected by PCR or by DEAFF test in a prospective study and, as expected, DEAFF failed to detect HCMV reactivation before disease in some patients. Furthermore, the incidence of HCMV disease and the associated mortality were reduced when GCV treatment was based on PCR positivity. In both groups therapy was continued until the clinical signs disappeared and PCR negativity was documented. No patient developed HCMV disease after cessation of therapy. Moreover there was a reduction in the duration and side effects of therapy especially in the PCR arm of the study.

Other investigators have chosen to use the HCMV antigenemia test as an early indication of HCMV infection; Boeckh *et al.*[99] conducted a randomized double-blind study comparing GCV prophylaxis with placebo. In patients with antigenemia, the study drug (i.e. placebo or GCV) was discontinued and GCV treatment given for at least three weeks or until the HCMV antigenemia test became negative, and was resumed only if antigenemia recurred. It was found that delaying the start of GCV until antigenemia occurred and discontinuing GCV based on negative antigenemia resulted in more HCMV disease before day 100 post-BMT than GCV prophylaxis. However, GCV prophylaxis was associated with more early invasive fungal infections and more late-onset HCMV disease (after cessation of GCV at day 100) resulting in similar survival rates.

Because of the problem with GCV toxicity, the usefulness of prophylactic foscarnet has been examined in several studies.[100-105] The first investigations[100-102] showed that prophylactic foscarnet is effective in preventing CMV disease (especially if used not only as an inpatient prophylaxis but also as outpatient treatment)[102] but nephrotoxicity seemed to be a limiting factor. Recently, several studies[103-105] have confirmed the initial reports. Bacigalupo *et al*.[103] demonstrated that HCMV prophylaxis with foscarnet, when compared with acyclovir prophylaxis, reduced the risk of developing HCMV antigenemia (91% versus 45%) and decreased transplant related mortality (TRM) (49% versus 13%); Ippoliti *et al*.[104] reported that foscarnet is a safe and effective agent for prevention of HCMV infection in allogeneic BMT recipients unable to receive GCV because of neutropenia; Ljungman *et al.*[105] have suggested that a lower, less toxic dose of foscarnet may be used for pre-emptive therapy without increasing the risk of development of HCMV disease; a controlled trial is indicated to evaluate fully the use of foscarnet in this context. A multicenter international study is currently in progress, comparing the efficacy of pre-emptive treatment with ganciclovir or foscarnet.

## Prevention of HCMV disease in VUD BMT recipients

An effective strategy for prevention of HCMV disease is essential after VUD BMT since these patients have a higher incidence of HCMV infection and disease compared with those receiving allografts from HLA-identical sibling donors.[26,34] Pre-emptive or prophylactic GCV is used in VUD BMT patients[35,99] despite the fact that very few studies specifically address the prevention of HCMV disease in VUD BMT recipients. However the small amount of data available suggests that the problem of HCMV disease after VUD BMT remains largely unsolved. Atkinson *et al*.[106] found that prophylactic GCV was less effective in the more heavily immunosuppressed HLA-identical VUD BMT patients than in HLA-identical sibling transplants. Stocchi *et al.*[107] found the probability of HCMV disease after VUD BMT to be 30% despite the use of prophylactic GCV, and pre-emptive GCV to be even less effective giving a probability of HCMV disease of 64% although survival was the same for both groups. Thus new strategies for prevention of HCMV disease are urgently needed after VUD BMT.

### *HCMV infection and disease in pediatric BMT recipients*

The epidemiology of HCMV infection in pediatric BMT recipients is not well defined. Most reports on transplant-related HCMV infections have not analyzed data on children separately. Meyers *et al*.[7] observed the rate of HCMV excretion and seroconversion to be 35% in children under the age of 10 years and over 50% in older age groups. The actuarial risk of HCMV antigenemia in children post-BMT was reported to be 51% at 120 days.[108] Some authors[109,110] evaluated the efficacy of HCMV prophylaxis on the incidence and clinical manifestations of HCMV infection in pediatric BMT recipients. One report[109] showed an incidence of HCMV excretion of 7.5 % using GCV at 30 mg/kg/week given 5 days per week. Campolat *et al*.[110] found a higher incidence of HCMV infection (54%) using GCV prophylaxis at a dose of 25 mg/kg/week given 5 days per week. Possible explanations could be a lower dose of GCV and a relatively high proportion of T-cell depleted and mismatched transplants in the latter report. GCV was well tolerated and only 27% of patients developed transient myelosuppression. In two other series of pediatric patients[108,111] a low incidence of neutropenia was also observed. In conclusion, in pediatric BMT recipients, as observed in adult patients, GCV prophylaxis is not usually adequate to prevent HCMV infection. However, these infections could be controlled by intensifying antiviral therapy or by initiating effective pre-emptive antiviral treatment at the first sign of infection.

## Conclusions

In conclusion, there is no evidence for the superiority of prophylactic over pre-emptive regimens since the overall survival is the same and the incidence of death from HCMV disease is similar.[99,107] Prophylaxis for late HCMV diseases is, however, needed especially in VUD BMT recipients. Some options for long-term prophylaxis might be continued suppression of viral replication with antiviral agents (GCV, foscarnet[103,104] or a combination of both[69]), or immunologic strategies such as restoration of HCMV-specific T-cell immunity by adoptive transfer of HCMV-specific T-cell clones[41] or boosting donor or patient immunity, using subunit vaccines such as gB or pp65.[112,113]

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*RS collected the literature data and wrote the manuscript. KNW helped in co-ordinating the project, and contributed to writing the manuscript. RF and MB co-ordinated the entire project. JA designed the study, co-ordinated the project, and contributed to writing the manuscript.*

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## References

1. Ho M. Epidemiology of cytomegalovirus infections. Rev Infect Dis 1990; 12:suppl.7:S701-10.
2. Taylor-Wiedeman J, Sissons JG, Borysiewicz LK, Sinclair JH. Monocytes are a major site of persistence of human cytomegalovirus in peripheral blood mononuclear cells. J Gen Virol 1991; 72:2059-64.
3. Minton EJ, Tysoe C, Sinclair JH, Sissons JG. Human cytomegalovirus infection of the monocytes/macrophages lineage in bone marrow. J Virol 1994; 68:4017-21.
4. Soderberg-Naucler C, Fish KN, Nelson JA. Reactivation of latent human cytomegalovirus by allogeneic stimulation of blood cells from healthy donors. Cell 1997; 91:119-26.
5. Mindelson M, Monard S, Sissons P, Sinclair J. Detection of endogenous human cytomegalovirus in CD34+ bone marrow progenitors. J Gen Virol 1996; 77:3099-102.
6. Michelson S. Interaction of human CMV with monocytes/macrophages: a love-hate relationship. Pathol Biol Paris 1997; 45:146-58.
7. Meyers JD, Flournoy N, Thomas ED. Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis 1986; 153:478-88.
8. Miller W, Flynn P, Mc Cullough J, et al. Cytomegalovirus infection after bone marrow transplantation: an association with acute graft versus host disease. Blood 1986; 67:1162-7.
9. Wingard JR, Chen DY, Burns WH, et al. Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. Blood 1988; 71:1432-7.
10. Meyers JD, Ljungman P, Fisher LD. Cytomegalovirus excretion as a predictor of cytomegalovirus disease after marrow transplantation: importance of cytomegalovirus viraemia. J Infect Dis 1990; 162:373-80.
11. Meyers JD, Flournoy N, Thomas ED. Nonbacterial pneumonia after allogeneic marrow transplantation: a review of ten years experience. Rev Infect Dis 1982; 4:1119-32.
12. Enright H, Haake R, Weisdorf D, et al. Cytomegalovirus pneumonia after bone marrow transplantation.Transplantation 1993; 55:1339-46.
13. Meyers JD, Spencer HC Jr, Watts JC, et al. Cytomegalovirus pneumonia after human marrow transplantation. Ann Intern Med 1975; 82:181-8.
14. Beschorner WE, Hutchins GM, Burns WH, Saral R, Tutschka JA, Santos GW. Cytomegalovirus pneumonia in bone marrow transplant recipients: miliary and diffuse patterns. Am Rev Respir Dis 1980; 122:107-14.
15. McDonald GB, Sharma P, Hackman RC, Meyers JD, Thomas ED. Esophageal infections in immunosuppressed patients after marrow transplantation. Gastroenterology 1985; 88:1111-7.
16. Spencer GD, Hackman RC, McDonald GB, et al. A prospective study of unexplained nausea and vomiting

after marrow transplantation. Transplantation 1986; 42:602-7.
17. Wingard JR, Piantadosi S, Burns WH, Zahurak ML, Santos GW, Saral R. Cytomegalovirus infections in bone marrow transplant recipients given intensive cytoreductive therapy. Rev Infect Dis 1990; 12:S793-804.
18. Winston DJ, Ho WG, Bartoni K, et al. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Ann Intern Med 1993; 118:179-84.
19. Prentice HG, Gluckman E, Powles RL, et al. For the European Acyclovir for CMV prophylaxis Study Group. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. Lancet 1994; 343:749-53.
20. Aschan J, Ringden O, Ljungman P, Lonnqvist B, Ohlman S. Foscarnet for treatment of cytomegalovirus infections in bone marrow transplant recipients. Scand J Infect Dis 1992;24:143-50.
21. Verdonck LF, van Heugten H, de Gast GC. Delay in platelet recovery after bone marrow transplantation: impact of cytomegalovirus infection. Blood 1985; 66:921-5.
22. Goodrich JM, Boeckh M, Bowden R. Strategies for the prevention of cytomegalovirus disease after marrow transplantation. Clin Infect Dis 1994; 19:287-98.
23. Hersman J, Meyers JD, Thomas ED, Buckner CD, Clift R. The effect of granulocyte transfusion on the incidence of cytomegalovirus infection after allogeneic marrow transplantation. Ann Intern Med 1982; 96: 149-52.
24. Bowden RA, Sayers M, Flournoy N, et al. Cytomegalovirus immune globulin and seronegative products to prevent primary cytomegalovirus infection after marrow transplantation. N Engl J Med 1986; 314:1006-10.
25. Winston DJ, Ho WG, Champlin RE. Cytomegalovirus infections after allogeneic bone marrow transplantation. Rev Infect Dis 1990; 12 (Suppl. 7):S776-92.
26. Marks DI, Culis JO, Ward KN, et al. Allogeneic bone marrow transplantation for chronic myeloid leukemia using siblings and volunteer unrelated donors. Ann Intern Med 1993; 119:207-14.
27. Li CR, Greenberg PD, Gilbert MJ, Goodrich JM, Riddel SR. Recovery of HLA-restricted cytomegalovirus (CMV)-specific T-cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. Blood 1994; 83: 1971-9.
28. Armitage JO. Bone marrow transplantation. N Engl J Med 1994; 330:827-38.
29. Speck B, Zwaan FE, Rood JJ, Eernisse JG. Allogeneic bone marrow transplantation in a patient with aplastic anaemia using a phenotypically HLA-identical unrelated donor. Transplantation 1973; 16:24-8.
30. Hansen JA, Clift RA, Thomas ED, Buckner CD, Storb R, Giblett ER. Transplantation of marrow from an unrelated donor to a patient with acute leukemia. N Engl J Med 1980; 303:565-7.
31. Hows JM, Yin JL, Marsh J, et al. Histocompatible unrelated volunteer donors compared with HLA nonidentical family donors in marrow transplantation for aplastic anaemia and leukemia. Blood 1986; 68: 1322-8.
32. Hows J, Bradley BA, Gore S, Downie T, Howard M, Gluckman E on behalf of the International Marrow Unrelated Search and Transplant (IMUST) Study: Prospective evaluation of unrelated donor bone marrow transplantation. Bone Marrow Transplant 1993; 12:371-80.
33. Ochs L, Shu XO, Miller J, et al. Late infections after allogeneic bone marrow transplantation: comparison of incidence in related and unrelated donor transplant recipients. Blood 1995;86:3979-86.
34. Takenaka K, Gondo H, Tanimoto K, et al. Increased incidence of cytomegalovirus (CMV) infection and CMV-associated disease after allogeneic bone marrow transplantation from unrelated donors. Bone Marrow Transplant 1997; 19:241-8.
35. Ward KN, Roberts IAG, van Rhee F. Ganciclovir and the prevention of CMV disease after allogeneic BMT: policy at the Hammersmith Hospital. Bone Marrow Transplant 1994; 13:230-1.
36. Meyers JD, Flournoy N, Thomas ED. Cytomegalovirus infection and specific cell-mediated immunity after marrow transplant. J Infect Dis 1980; 142:816-24.
37. Quinnan GU, Kirmani N, Rook AH, et al. Cytotoxic T cells in cytomegalovirus infection: HLA restricted T lymphocyte and non T lymphocyte cytotoxic responses correlate with recovery from cytomegalovirus infection in bone marrow transplant recipients. N Engl J Med 1982; 307:7-13.
38. Ljungman P, Lonnqvist B, Wahren B, et al. Lymphocyte responses after cytomegalovirus infection in bone marrow transplant recipients: a 1 year follow-up. Transplantation 1985; 40:515-20.
39. Reusser P, Riddell S, Meyers J, Greenberg PD. Cytotoxic T-lymphocyte response to cytomegalovirus after human allogeneic bone marrow transplantation: pattern of recovery and correlation with cytomegalovirus infection and disease. Blood 1991; 78:1373-80.
40. Quinnan GV, Kirmani N, Rook AH, et al. HLA-restricted T lymphocyte and non-T-lymphocyte cytotoxic responses correlate with recovery from cytomegalovirus infection in bone marrow transplant recipients. N Eng J Med 1982; 307:7-13.
41. Riddell SR, Watanabe KS, Goodrich JM, Li CR, Agha ME, Greenberg PD. Restoration of viral immunity in immunodeficient humans by adoptive transfer of T cell clones. Science 1992; 257:238-41.
42. Riddell SR, Greenberg PD. Therapeutic reconstitution of human viral immunity by adoptive transfer of cytotoxic T lymphocyte clones. Curr Top Microbiol Immunol 1994; 189:9-34.
43. Krause H, Hebart H, Jahn G, Muller CA, Einsele H. Screening for CMV-specific T cell proliferation to identify patients at risk of developing late onset CMV disease. Bone Marrow Transplant 1997; 19:1111-6.
44. Ljungman P, Aschan J, Azinge JN, et al. Cytomegalovirus viraemia and specific T-helper cell responses as predictors disease after allogeneic marrow transplantation. Br J Hematol 1993: 83:118-24.
45. Heagy W, Crumpacker C, Lopez PA, Finberg RA. Inhibition of immune functions by antiviral drugs. J Clin Invest 1991; 87:1916-23.
46. Tocci MJ, Livelli TJ, Perry HC, Crumpacker CS, Field AK. Effect of nucleoside analog 2'-nor-2'-deoxyguanosine on human cytomegalovirus replication. Antimicrob Ag Chem 1983; 25:247-55.
47. Riddell S R, Rabin M, Geballe AP, Britt WJ, Greenberg PD. Class I MHC-restricted cytotoxic T lymphocyte recognition of cells infected with human cytomegalovirus does not require endogenous viral gene expression. J Immunol 1991; 146:2795-800.
48. Winston DJ, Gale RP. Prevention and treatment of cytomegalovirus infection and disease after bone marrow transplantation in the 1990s. Bone Marrow Transplant 1991; 8:7-11.
49. Weiner RS, Bortin MM, Gale RP, et al. Interstitial pneumonitis after bone marrow transplantation. Ann Intern Med 1986; 104:168-75.
50. Cheung KS, Lang DJ. Transmission and activation of cytomegalovirus with blood transfusion: a mouse

model. J Infect Dis 1977; 135:841-5.
51. Braun RW, Reiser HC. Replication of human cytomegalovirus in human peripheral blood T cells. J Virol 1986; 60:29-36.
52. Klein HG. Wolf in wolf's clothing: is it time to raise the bounty on the passenger leukocyte? Blood 1992; 80:1865-8.
53. Martin PJ. Increased disparity for minor histocompatibility antigens as a potential cause of increased GvHD risk in marrow transplantation from unrelated donors compared with related donors. Bone Marrow Transplant. 1991; 8:217-23.
54. Beatty PG, Anasetti C, Hansen JA, et al. Marrow transplantation from unrelated donors for treatment of hematologic malignancies: effect of mismatching for one HLA locus. Blood 1993; 81:249-53.
55. Petersdorf EW, Smith AG, Mickelson EM, et al. The role of HLA-DPB1 disparity in the development of acute graft-versus-host disease following unrelated donor marrow transplantation. Blood 1993; 81:1923-32.
56. Wade JC, Hintz M, McGuffin RW, Springmeyer SC, Connor JD, Meyers JD. Treatment of cytomegalovirus pneumonia with high-dose acyclovir. Am J Med 1982; 73:249-56.
57. Tyms AS, Davis JM, Jeffries DJ, Meyers JD. BWB759U, an analogue of acyclovir, inhibits human cytomegalovirus in vitro. Lancet 1984; 2:924-5.
58. Shepp DH, Dandliker PS, de Miranda P, et al. Activity of 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine in the treatment of cytomegalovirus pneumonia. Ann Intern Med 1985; 103:368-73.
59. Reed EC, Bowden RA, Dandliker PS, et al. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplant. Ann Intern Med 1988; 109:783-8.
60. Emanuel D, Cunningham I, Jules-Elysee K, et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with a combination of ganciclovir and high dose intravenous immunoglobulin. Ann Intern Med 1988; 109:777-82.
61. Schmidt GM, Kovacs A, Zaia JA, et al. Ganciclovir/immunoglobulin combination therapy for the treatment of human CMV-associated interstitial pneumonitis in bone marrow allograft recipients. Transplantation 1988; 46:905-7.
62. Helgstrand E, Eriksson B, Johansson NG, et al. Trisodium phosphonoformate, a new antiviral conpound. Science 1978; 201:819-21.
63. Reno JM, Lee LF, Boezi JA. Inhibition of herpesvirus replication and herpesvirus-induced deoxyribonucleic acid polymerase by phosphonoformate. Antimicrob Agents Chemother 1978; 13:188-92.
64. Apperley JF, Marcus RE, Goldman JM, Wardle DG, Gravett PJ, Chanas A. Foscarnet for cytomegalovirus pneumonitis [letter]. Lancet 1985; May 18:1151.
65. Ringden O, Wilczek H, Lonnqvist B, Gahrton G, Wahren B, Lernestedt JO. Foscarnet for cytomegalovirus infections [letter]. Lancet 1985; June 29:1503-4.
66. Akesson-Johansson A, Lernestedt JO, Ringden O, Lonnqvist B, Wahren B. Sensitivity of cytomegalovirus to intravenous foscarnet treatment. Bone Marrow Transplant 1986;1:215-20.
67. Ringden O, Lonnqvist B, Paulin T, et al. Pharmacokinetics, safety and preliminary clinical experiences using foscarnet in the treatment of cytomegalovirus infections in bone marrow and renal transplant recipients. J Antimicrob Chemother 1986; 17:373-87.
68. Drobyski WR, Knox K, Carrigan DR, Ash RC. Foscarnet therapy of ganciclovir-resistant cytomegalovirus in marrow transplantation. Transplantation 1991; 52: 155-7.
69. Bacigalupo A, Bregante S, Tedone E, et al. Combined foscarnet-ganciclovir treatment for cytomegalovirus infections after allogeneic hemopoietic stem cell transplantation. Transplantation 1996; 62:376-80.
70. Boivin G, Chan S, Querk MR, Erice A, Jordan MC. Detection of ganciclovir resistance mutations quantification of cytomegalovirus DNA in leukocytes of patients with fatal disseminated CMV disease. J Infect Dis 1996; 173:523-8.
71. Lipson SM, Soni M, Biondo FX, Shepp DH, Kaplan MH, Sun T. Antiviral susceptibility testing-flow cytometric analysis (AST-FCA) for the detection of CMV drug resistance. Diagn Microbiol Infect Dis 1997; 28: 123-9.
72. Griffiths PD, Stirk PR, Ganczakowski M, et al. Rapid diagnosis of cytomegalovirus infection in immunocompromised patients by detection of early antigen fluorescent foci. Lancet 1984; ii:1242-4.
73. van Der Bij W, Torensma R, Van Son JW, et al. Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leukocytes. J Med Virol 1988; 25:179-88.
74. van der Bij W, Schirm J, Torensma R, van Son WJ, Tegzess AM, de The TH. Comparison between viremia and antigenemia for detection of cytomegalovirus in blood. J Clin Microbiol 1988; 26:2531-5.
75. Jiwa NM, van Gemert GW, Rapp AK, et al. Rapid detection of human cytomegalovirus DNA in peripheral blood leukocytes of viraemic transplant recipients by polymerase chain reaction. Transplantation 1989; 48:72-6.
76. Einsele H, Ehninger G, Hebart H, 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; 86:2815-20.
77. Goodrich JM, Mori M, Gleaves CA, et al. Early treatment with ganciclovir to prevent cytomegalovirus disease after allogeneic bone marrow transplantation. N Engl J Med 1991; 325:1601-7.
78. de The' TH, van der Ploeg M, van der Berg AP, et al. Direct detection of cytomegalovirus in peripheral blood leukocytes: a review of the antigenemia assay and polymerase chain reaction. Transplantation 1992; 54:193-8.
79. Vlieger AM, Boland GJ, Jiwa NM, et al. Cytomegalovirus antigenemia assay or PCR can be used to monitor ganciclovir treatment in bone marrow transplant recipients. Bone Marrow Transplant 1992; 9: 247-53.
80. Boeckh M, Bowden RA, Goodrich JM, et al. Cytomegalovirus antigen detection in peripheral blood leukocytes after allogeneic bone marrow transplantation. Blood 1992; 80:1358-64.
81. Gondo H, Minematsu T, Harada M, et al. Cytomegalovirus (CMV) antigenaemia for rapid diagnosis and monitoring of CMV-associated disease after bone marrow transplantation. Br J Haematol 1994; 86:130-7.
82. de The' TH, van der Bij W, van der Berg AP, et al. Cytomegalovirus antigenemia. Rev Infect Dis 1990; 12(Suppl. 7):S737-44.
83. Revello MG, Percivalle E, Zavattoni M, et al. Detection of human cytomegalovirus immediate-early antigen in leukocytes as a marker of viremia in immunocompromised patients. J Med Virol 1989; 29:88-93.
84. Schmidt CA, Oettle H, Wilborn F, et al. Demonstration of cytomegalovirus after bone marrow transplantation by polymerase chain reaction, virus culture and antigen detection in buffy coat leukocytes. Bone Marrow Transplant 1994; 13:71-5.
85. Einsele H, Steidle M, Vallbracht A, Saal JG, Ehninger

G, Muller CA. Early occurrence of human cytomegalovirus infection after bone marrow transplantation as demonstrated by the Polymerase Chain Reaction technique. Blood 1991; 77:1104-10.
86. Hebart H, Muller C, Loffler J, Jahn G, Einsele H. Monitoring of cytomegalovirus infection: a comparison of PCR from whole blood, plasma-PCR, pp65-antigenemia and virus culture in patients after bone marrow transplantation. Bone Marrow Transplant 1996; 17: 861-8.
87. Goto H, Yuasa K, Sakamaki H, et al. Rapid detection of CMV pneumonia in recipients of bone marrow transplant: evaluation and comparison of 5 survey methods for bronchoalveolar lavage fluid. Bone Marrow Transplant 1996; 17:855-60.
88. Stanier P, Taylor DL, Kitchen AD, Wales N, Tryhorn Y, Tyms AS. Persistence of cytomegalovirus in mononuclear cells in peripheral blood from blood donors. Br Med J 1989; 299:897-8.
89. Gerna G, Furione M, Baldanti F, Percivalle E, Comoli P, Locatelli F. Quantitation of human cytomegalovirus DNA in bone marrow transplant recipients. B J Haematol 1995; 91:674-83.
90. Guglielmo BJ, Wong-Beringer A, Linker CA. Immune globulin therapy in allogeneic bone marrow transplant: a critical review. Bone Marrow Transplant 1994; 13:499-510.
91. Miller WJ, McCullough J, Balfour HH, et al. Prevention of cytomegalovirus infection following bone marrow transplantation: a randomised trial of blood product screening. Bone Marrow Transplantation 1991; 7: 227-34.
92. Bowden RA, Slichter SJ, Sayers MH, et al. A comparison of filtered leukocytes-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplantation. Blood 1995; 86:3598-603.
93. Meyers JD, Reed EC, Shepp DH, et al. Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 1988; 318:70-5.
94. Schmidt GM, Horak DA, Niland JC, Duncan SR, Forman SJ, Zaia JA. A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplant. N Engl J Med 1991; 324:1005-11.
95. Atkinson K, Downs K, Golenia M, et. al. Prophylactic use of ganciclovir in allogeneic bone marrow transplantation: absence of clinical cytomegalovirus infection. Br J Haematol 1991; 79: 57-62.
96. Yau J, Dimopoulos MA, Huan SD, et al. Prophylaxis of cytomegalovirus infection with ganciclovir in allogeneic marrow transplantation. Eur J Haematol 1991; 47:371-6.
97. von Bueltingsloewen A, Bordigoni P, Witz F, et al. Prophylactic use of ganciclovir for allogeneic bone marrow transplant recipients. Bone Marrow Transplant 1991; 325:1601-7.
98. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 1993; 118:173-8.
99. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. Blood 1996; 88:4063-71.
100. Ringden O, Lonnqvist B, Aschan J, Sundberg B. Foscarnet prophylaxis in marrow transplant recipients [letter]. Bone Marrow Transplant 1989; 4:713.
101. Reusser P, Gambertoglio JG, Lilleby K, Meyers JD. Phase I-II trial of foscarnet for prevention of cytomegalovirus infection in autologous and allogeneic marrow transplant recipients. J Infect Dis 1992; 166:473-9.
102. Lonnqvist B, Aschan J, Ringden O. Foscarnet as inpatient prophylaxis only is insufficient to prevent cytomegalovirus infection after marrow transplantation. J Infect Dis 1993; 168:1073.
103. Bacigalupo A, Tedone E, Van Lint MT, et al. CMV prophylaxis with foscarnet in allogeneic bone marrow transplant recipients at high risk of developing CMV infections. Bone Marrow Transplant 1994; 13:783-8.
104. Ippoliti C, Morgan A, Warkentin D, et al. Foscarnet for prevention of cytomegalovirus infection in allogeneic marrow transplant recipients unable to receive ganciclovir. Bone Marrow Transplant 1997; 20:491-5.
105. Ljungman P, Oberg G, Aschan J, et al. Foscarnet for pre-emptive therapy of CMV infection detected by a leukocyte-based nested PCR in allogeneic bone marrow transplant patients. Bone Marrow Transplant 1996; 18:5665-8.
106. Atkinson K, Arthur C, Bradstock K, et al. Prophylactic ganciclovir is more effective in HLA-identical family member marrow transplant recipients than in more heavily immune suppressed HLA-identical unrelated donor marrow transplant recipients. Bone Marrow Transplant 1995; 16:401-5.
107. Stocchi R, Szydlo R, Craddock C, et al. A comparison of prophylactic versus pre-emptive ganciclovir to prevent cytomegalovirus disease after volunteer unrelated donor bone marrow transplant. Bone Marrow Transplant 1998; in press.
108. Locatelli F, Percivalle E, Comoli P, et al. Human cytomegalovirus infection in pediatric patients given allogeneic bone marrow transplantation: role of early antiviral treatment of HCMV antigenemia on patient's outcome. Br J Haematol 1994; 88:64-71.
109. Onbluetzingsloewen A, Bordigoni P, Witz F, et al. Prophylactic use of ganciclovir for allogeneic bone marrow transplant recipients. Bone Marrow Transplant 1993; 12:197-202.
110. Campolat C, Culbert S, Gardner M, Whimbey E, Tarrand J, Chan KW. Ganciclovir prophylaxis for cytomegalovirus infection in pediatric allogeneic bone marrow transplant recipients. Bone Marrow Transplant 1996; 17:589-93.
111. Roberts WD, Weinberg KI, Kohn DB, et al. Granulocyte recovery in pediatric marrow transplant recipients treated with ganciclovir for cytomegalovirus infection. Am J Pediatr Hematol Oncol 1993; 15:320-3.
112. Gonczol E, Ianacone J, Ho W, Starr S, Meignier B, Plotkin S. Isolated gA/gB glycoprotein complex of human cytomegalovirus envelopes induces humoral and cellular immune-responses in human volunteers. Vaccine 1990; 8:130-6.
113. McLaughlin-Taylor E, Pande H, Forman SJ, et al. Identification of the major late human cytomegalovirus matrix protein pp65 as a target antigen for CD8+ virus-specific CTL. J Med Virol 1994; 43:103-10.