**Name of Journal: *World Journal of Transplantation***

**ESPS Manuscript NO: 20447**

**Manuscript Type: Minireviews**

**Cytomegalovirus infection in the bone marrow transplant patient**

Bhat V *et al.* CMV in stem cell transplant

**Vivek Bhat, Amit Joshi, Rahul Sarodem, Preeti Chavan**

**Vivek Bhat**, **Amit Joshi**, **Preeti Chavan,** Advanced centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai 410210, India

**Rahul Sarode,** Tata Memorial Hospital, Navi Mumbai 410210, India

**Author contributions:** Bhat V and Sarodem R wrote the manuscript; Joshi A and Chavan P edited and finalised the manuscript.

**Conflict-of-interest** **statement:** The authors declare no conflicts of interest regarding this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Dr.** **Amit Joshi MD, DM**, Advanced centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Dr. E Borges Road, Parel, Navi Mumbai 410210, India. dramit74@yahoo.com

**Telephone:** +91-22-27405000

**Fax:** +91-22-27405093

**Received:** June 5, 2015

**Peer-review started:** June 5, 2015

**First decision:** August 10, 2015

**Revised:** October 17, 2015

**Accepted:** November 13, 2015

**Article in press:**

**Published online:**

**Abstract**

Cytomegalovirus (CMV) infection is an important contributor to the morbidity and mortality associated with Bone marrow transplantation (BMT). Infection may lead to CMV disease involving multiple organs such as pneumonia, gastroenteritis, retinitis, CNS involvement and others. CMV seropositivity is an important risk factor and approximately half of BMT recipients will develop clinically significant infection most commonly in the first 100 d post-transplant. The commonly used tests to diagnose CMV infection in these patients include the pp65 antigenemia test and the CMV DNA PCR assay. Because of its greater sensitivity and lesser turnaround time, the CMV PCR is nowadays the preferred test and serves as a main guide for pre-emptive therapy. Methods of CMV prevention include use of blood products from seronegative donors or leukodepleted products. Prophylaxis or pre-emptive therapy strategies for CMV prevention may be used post-transplant with the latter becoming more common. The commonly used antivirals for pre-emptive therapy and CMV disease management include intravenous gancyclovir and foscarnet. The role of intravenous immunoglobulin, although used commonly in CMV pneumonia is not clear.

**Key words:** Cytomegalovirus; Infection; Bone marrow transplant

**Core tip:** Cytomegalovirus (CMV) infection and CMV disease may be associated with serious complications in the bone marrow transplant patient. The most commonly used test to monitor CMV replication is the CMV DNA polymerase chain reaction assay and serves a guide for preemptive therapy. Gancyclovir followed by foscarnet are most commonly used in CMV management.

Bhat V, Joshi A, Sarodem R, Chavan P. Cytomegalovirus infection in the bone marrow transplant patient. *World J Transplant* 2015; In press

**INTRODUCTION**

Cytomegalovirus (CMV) is a member from betaherpesvirinae subfamily. CMV is the largest virus among all herpes virus, with the size of 150-200 nm, containing a linear double stranded DNA molecule in its nucleocapsid[1]. CMV has tendency to cause prolonged latent infection with characteristic enlargement of infected cell with prominent intranuclear inclusion bodies. CMV can infect several types of body cells such as epithelial cells, haematopoietic cell, and connective tissue[2]. Cytomegalovirus has a wide spectrum of clinical presentation. It can present generally as asymptomatic and persistent infections in healthy individuals however, it can also lead to serious disorders among transplant recipients, immunodeficient patients and patients on immunosuppressive treatment[3]. CMV infection can appear as primary infection, reinfection or reactivation. Incidence of CMV infection is increasing, as the number of immunocompromised patients is increasing, especially in transplant cases. CMV infection is a major problem in allogeneic bone morrow transplant (BMT) cases, 30%-50% cases show clinically significant infection[4]. Human leucocyte matched(HLA) transplantation is preferred for prevention of adverse outcome, but haploidentical stem cell transplantation (Haplo-SCT) can be used as an alternative for transplantation candidate lacking HLA matched donors[5]. One major drawback of Haplo-SCT is impaired recovery of adoptive immunity,which adversely affects treatment outcome by increasing the chances of CMV, fungal and bacterial infections[6]. Regardless of the prior seropositive status of donor or recipient, 32%-70% cases can acquire CMV infection after allogeneic BMT[1]. There is more risk of acquiring CMV infection in first 3-4 mo of transplantation[7]. CMV infection is generally seen in immediate to late post engraftment period.

***Pathogenesis***

CMV can ubiquitously infect any cell in human body. CMV infection to endothelial cells and haematopoietic cells will lead to systemic spread of infection[8]. Arterial vasculature remains the most common site for harbouring latent CMV[9]. Its pathogenesis is a highly complex involving human leukocyte antigens, various endothelial adhesion molecules and cytokines[10]. In immunocompetent individuals CMV infections generally remains asymptomatic and virus persist in body in latent stage[11]. Majority of CMV infections in transplant cases are due to reactivation of virus from its latent stage[12]. In adults immune reconstitution following transplantation depends mainly upon peripheral expansion of mature T lymphocytes in the allograft because of poor thymic functioning. The process of immunr reconstitution is influenced by age, HLA disparity, source of stem cells and graft composition, various conditioning regimens and steroid administration[5].The serological status of the transplant recipient is a significant risk factor for CMV reactivation in bone morrow transplant cases[13]. Other studies also showed that serology status of recipient remains the predominant risk factor for BMT rejection[14,15] and associated mortality. Host immune system recognises virion after infection, and lead to activation of host immune system. Several studies have reported that after bone marrow transplantation CD-4 T cells regenerate relatively at slow rate, which subsequently provide limited help to cytotoxic T cells for control of CMV replication[16,17]. Patients undergoing Haplo-SCT have higher incidence of CMV antigenemia than HLA matched transplantation[18].Other risk factors for CMV infections in hematopoietic stem cell transplantation (HSCT) cases are advancing age, immunosuppresion because of whole body irradiation, antithymocyte globulins, chemotherapeutic regimens and transplantation of umbilical cord blood[19,20]. Recipient of non- myeloablative (HSCT) are more prone to have late CMV infection, mostly due to chemotherapy containing alemtuzumab or antilymphocyte globulins[20].

***Clinical manifestations***

Infection with CMV is a major cause for morbidity and mortality in immunocompromised patients, particularly in transplant recipients[21,22]. The following clinical types are commonly recognized.

**CMV pneumonia:** CMV pneumonia is a potentially fatal disease with non specific symptoms in most of the cases[22]. Incidence of CMV pneumonia is showing a decreasing trend because of the effective use of anti-viral prophylaxis or pre-emptive therapy after HSCT[24]. Among autologous recipient incidence is about 1%-6% and among allogeneic recipients it is high, around 10%-30%[25]. Diagnosis of CMV pneumonia is based on clinical and radiological evidences. In addition microbiologically CMV can be detected in blood, BAL or in lung tissue. Immunohistochemical staining for viral identification or demonstration of its inclusion body in lung biopsy is a gold standard investigation, but biopsy is not always a feasible option in such cases[26]. As compared to pre-antiviral era, mortality rate of CMV pneumonia is reduced to less than 50% because of use of specific antivirals or high dosage of immnuoglobulins (0.2–0.5 mg/kg per day)[23].

***Gastrointestinal infections***

Incidence rate of CMV gastrointestinal (GI) infections is around 2%, usually observed within one to two year of transplantation[27]. It is an ulcerative condition which can occur anywhere along whole GI tract; however upper GI tract involvement is more common in patients with haematological malignancies or in patients after BMT[28].

CMV esophagitis commonly present with odynophagia and dysphagia. Endoscopic examination reveals characteristic ulceration which is confirmed by presence of CMV inclusion bodies[29]. CMV gastritis presents with severe and continuous epigastric pain. Colorectal involvement is more commonly seen in BMT patients[28]. CMV colitis generally presents with diarrhea, abdominal pain, anorexia and fever. Colonic perforation, haemorrhage and peritonitis can occur as a complication of CMV colitis[30].

***Central nervous system (CNS) infections***

CNS involvement is seen in patients with profound immunodeficiency disorder as BMT or AIDS patients[31]. CMV CNS involvement is generally seen in late stage of diseases[32]. It presents with rapid progression of cognitive disorder along with cranial nerve palsies[33]. Diagnosis is generally made by radiological investigation and PCR for detection of CMV in CSF is a useful tool for its diagnosis[32].

***CMV retinitis***

CMV retinitis is present as late complication after BMT. It account for 5% of all late CMV manifestation[34]. It is a slow progressive disorder which generally starts from peripheral site of retina, causing minimal damage to visual abilities of patients in early stage of infection[35]. Lymphopenia is an important risk factor for development of CMV retinitis. PCR on aqueous humour can be used as diagnostic tool in ophthalmic manifestations[36].

***Miscellaneous disorders***

Cystitis, nephritis, myocarditis, pancreatitis can also be rarely seen in patients with CMV infection in BMT cases[37].

***Diagnosis***

Several diagnostic methods are available for diagnostic surveillance of patients at risk of acquiring CMV infection. Methods that have been described for detection of CMV infection include serological tests for detection of antigens or antibodies, viral culture and quantitative or qualitative CMV genomic detection from various body fluids like blood, urine or broncoalveolar lavage[38]. The common tests used in HSCT patients include pp65 antigenemia and the CMV DNA PCR. Monitoring of viral levels is important to guide preemptive therapy. The pp65 antigen test detects the CMV antigens on mononuclear cells in peripheral blood but its limitations include subjectivity and a relative lack of standardization, labour intensive nature of the test and lesser sensitivity as compared to PCR[39,40]. Various techniques used for detection of CMV viral load have been proven to be useful as a prognostic indicator and allowing monitoring of antiviral treatment[41,42]. Highly conserved regions of CMV such as US 17, UL 50, US 54, LC 342, LC 383 and the immediate early (IE) gene have been used as primer targets for the CMV PCR assay[38,43].The advantages of real time RCR for detection of CMV in whole blood and plasma is that it is automated, more sensitive[39],has a reasonably limited turnaround time and has replaced the pp65 antigenemia assay in most centres.

***Prevention of CMV***

Prevention of CMV infection and disease is an important component of post transplant monitoring and management. Serum CMV IgG levels must be determined to know the baseline status of the recipient before the transplant. CMV negative allogeneic recipients must receive blood products from CMV negative donors or leucodepleted blood products[44], the same is also recommended for autologous patients. Strategies such as prophylactic or preemptive therapy have been advocated in allogeneic patients[45]. In prophylactic therapy, Gancyclovir, acyclovir, valacyclovir and forcarnet have been shown to be effective. When laboratory support in the form of availability of sensitive rapid molecular tests such as CMV DNA PCR is available, the pre-emptive strategy is preferable and most centres now prefer this approach[46,47]. Patients must be screened for viremia or antigenemia once a week from days 10-100[45]. Many centres use a cut–off of 1000/mL copies of CMV DNA or a fivefold rise of baseline levels (whichever is lower) as the threshold for initiating preemptive therapy. Gancyclovir is most commonly used followed by foscarnet and cidofovir[48,49]. Ganciclovir (GCV) is a nucleotide analogue which by catalysing CMV DNA polymerase action, competitively inhibits CMV DNA synthesis. The therapy may be given for 2 wk or till the virus falls to below detection levels or up to d-100[34].In early phase of HSCT, Ganciclovir therapy can lead to neutropenia and thrombocytopenia. Antiviral resistance must be suspected if antigenemia or CMV DNA levels continue to increase after 2 wk of therapy. The genotype of the infecting CMV strain can be tested and Second line drugs must be considered[24]. Foscarnet is preferred in cases with myelosuppression or known GCV resistancebut nephrotoxicity which may lead to acute renal failure or electrolyte abnormality is a major limiting factor[50]. Cidofovir is a third line agent for CMV, but again, myelotoxicity and nephrotoxicity are major side effects.

***Treatment of CMV disease***

Gastrointestinal CMV is generally treated with intravenous gancyclovir for several weeks; alternatively foscarnet may also be used[24].Current standard of care for CMV pneumonia involves the use of the above mentioned drugs along with intravenous immunoglobulin (IVIG). However the supposed beneficial role of CMV specific immunoglobulin or polled IVIG is still not clear from available studies[51,52]. CMV retinitis and other manifestation of CMV in the BMT patient are also usually treated with IV gancyclovir and foscarnet[47].

***Future perspectives***

There is a need to further standardize and evolve a consensus on the frequency and cut off values of viral load estimations used in pre-emptive therapy. Newer drugs such as maribavir, are under trail and would be indicated in case of toxicity and/or resistance to the conventional antivirals[47]. Maribavir in high dosage can be used for treatment of resistant cases[53]. Maribavir does not cause myelosuppression. Immune augmentation by using transfer of donor derived CMV specific T-cells have shown promising response in refractory cases without significant toxicity[54]. The anti CMV effect of drugs like artisunate and sirolimus also need to be further explored[24]. Tests to detect antiviral resistance should be available more easily. Larger studies are indicated to clearly define the role of IVIG in CMV disease treatment. Further research and development in the above mentioned areas would improve the management of CMV in the HSCT patient.

**REFERENCES**

1 **Landolfo S**, Gariglio M, Gribaudo G, Lembo D. The human cytomegalovirus. *Pharmacol Ther* 2003; **98**: 269-297 [PMID: 12782241 DOI: 10.1016/S0163-7258(03)00034-2]

2 **Minton K**. Viral immunity: How CMV bypasses immune memory. *Nat Rev Immunol* 2010; **10**: 288 [PMID: 20425915 DOI: 10.1038/nri2768]

3 **Griffiths PD**. Cytomegalovirus. In: Zuckerman AJ, Banatvala JE, Pattison JR. Principles and Practice of Clinical Virology. London: John Wiley and Sons, 2000: 79-116

4 **Sissons JG**, Carmichael AJ. Clinical aspects and management of cytomegalovirus infection. *J Infect* 2002; **44**: 78-83 [PMID: 12076065 DOI: 10.1053/jinf.2001.0949]

5 **Luo XH**, Chang YJ, Huang XJ. Improving cytomegalovirus-specific T cell reconstitution after haploidentical stem cell transplantation. *J Immunol Res* 2014; **2014**: 631951 [PMID: 24864269 DOI: 10.1155/2014/631951]

6 **George B**, Pati N, Gilroy N, Ratnamohan M, Huang G, Kerridge I, Hertzberg M, Gottlieb D, Bradstock K. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. *Transpl Infect Dis* 2010; **12**: 322-329 [PMID: 20487414 DOI: 10.1111/j.1399-3062.2010.00504.x]

7 **Zaia JA**. Cytomegalovirus infections. In: Thomas ED, Blume KG, Forman SJ. Hematopoietic Cell Transplantation. Malden: Blackwell Science, 1998: 560-583

8 **Sinzger C**, Digel M, Jahn G. Cytomegalovirus cell tropism. *Curr Top Microbiol Immunol* 2008; **325**: 63-83 [PMID: 18637500]

9 **Melnick JL**, Petrie BL, Dreesman GR, Burek J, McCollum CH, DeBakey ME. Cytomegalovirus antigen within human arterial smooth muscle cells. *Lancet* 1983; **2**: 644-647 [PMID: 6136795 DOI: 10.1016/S0140-6736(83)92529-1]

10 **Nichols WG**, Corey L, Gooley T, Davis C, Boeckh M. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. *J Infect Dis* 2002; **185**: 273-282 [PMID: 11807708 DOI: 10.1086/338624]

11 **Borchers AT**, Perez R, Kaysen G, Ansari AA, Gershwin ME. Role of cytomegalovirus infection in allograft rejection: a review of possible mechanisms. *Transpl Immunol* 1999; **7**: 75-82 [PMID: 10544437 DOI: 10.1016/S0966-3274(99)80023-9]

12 **Pillay D**, Webster A, Prentice HG, Griffiths PD. Risk factors for viral reactivation following bone marrow transplantation. *Ann Hematol* 1992; **64** Suppl: A148-A151 [PMID: 1322187]

13 **Lin TS**, Zahrieh D, Weller E, Alyea EP, Antin JH, Soiffer RJ. Risk factors for cytomegalovirus reactivation after CD6+ T-cell-depleted allogeneic bone marrow transplantation. *Transplantation* 2002; **74**: 49-54 [PMID: 12134098]

14 **Saavedra S**, Jarque I, Sanz GF, Moscardó F, Jiménez C, Martín G, Plumé G, Regadera A, Martínez J, De La Rubia J, Acosta B, Pemán J, Pérez-Bellés C, Gobernado M, Sanz MA. Infectious complications in patients undergoing unrelated donor bone marrow transplantation: experience from a single institution. *Clin Microbiol Infect* 2002; **8**: 725-733 [PMID: 12445010 DOI: 10.1046/j.1469-0691.2002.00458.x]

15 **George B**, Mathews V, Srivastava A, Chandy M. Infections among allogeneic bone marrow transplant recipients in India. *Bone Marrow Transplant* 2004; **33**: 311-315 [PMID: 14647246 DOI: 10.1038/sj.bmt.1704347]

16 **La Rosa C**, Diamond DJ. The immune response to human CMV. *Future Virol* 2012; **7**: 279-293 [PMID: 23308079 DOI: 10.2217/fvl.12.8]

17 **Aubert G**, Hassan-Walker AF, Madrigal JA, Emery VC, Morte C, Grace S, Koh MB, Potter M, Prentice HG, Dodi IA, Travers PJ. Cytomegalovirus-specific cellular immune responses and viremia in recipients of allogeneic stem cell transplants. *J Infect Dis* 2001; **184**: 955-963 [PMID: 11574909 DOI: 10.1086/323354]

18 **Lu DP**, Dong L, Wu T, Huang XJ, Zhang MJ, Han W, Chen H, Liu DH, Gao ZY, Chen YH, Xu LP, Zhang YC, Ren HY, Li D, Liu KY. Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. *Blood* 2006; **107**: 3065–3073 [PMID: 16380454]

19 **Cummins NW**, Deziel PJ, Abraham RS, Razonable RR. Deficiency of cytomegalovirus (CMV)-specific CD8+ T cells in patients presenting with late-onset CMV disease several years after transplantation. *Transpl Infect Dis* 2009; **11**: 20-27 [PMID: 18811629 DOI: 10.1111/j.1399-3062.2008.00344.x.]

20 **Ozdemir E**, Saliba RM, Champlin RE, Couriel DR, Giralt SA, de Lima M, Khouri IF, Hosing C, Kornblau SM, Anderlini P, Shpall EJ, Qazilbash MH, Molldrem JJ, Chemaly RF, Komanduri KV. Risk factors associated with late cytomegalovirus reactivation after allogeneic stem cell transplantation for hematological malignancies. *Bone Marrow Transplant* 2007; **40**: 125-136 [PMID: 17530009 DOI: 10.1038/sj.bmt.1705699]

21 **Dummer JS**, Hardy A, Poorsattar A, Ho M. Early infections in kidney, heart, and liver transplant recipients on cyclosporine. *Transplantation* 1983; **36**: 259-267 [PMID: 6310832]

22 **Singh N**, Dummer JS, Kusne S, Breinig MK, Armstrong JA, Makowka L, Starzl TE, Ho M. Infections with cytomegalovirus and other herpesviruses in 121 liver transplant recipients: transmission by donated organ and the effect of OKT3 antibodies. *J Infect Dis* 1988; **158**: 124-131 [PMID: 2839576 DOI: 10.1093/infdis/158.1.124]

23 **Vigil KJ**, Adachi JA, Chemaly RF. Viral pneumonias in immunocompromised adult hosts. *J Intensive Care Med* 2010; **25**: 307-326 [PMID: 20837633 DOI: 10.1177/0885066610377969]

24 **Boeckh M**, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood* 2009; **113**: 5711-5719 [PMID: 19299333 DOI: 10.1182/blood-2008-10-143560]

25 **Kotloff RM**, Ahya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2004; **170**: 22-48 [PMID: 15070821 DOI: 10.1164/rccm.200309-1322SO]

26 **Zhao XS**, Liu DH, Xu LP, Chen H, Chen YH, Zhang XH, Han W, Wang Y, Liu KY, Huang XJ. [Clinical features of cytomegalovirus pneumonia after allogeneic hematopoietic stem cell transplantation]. *Beijing Da Xue Xue Bao* 2009; **41**: 548-553 [PMID: 19829672]

27 **van Burik JA**, Lawatsch EJ, DeFor TE, Weisdorf DJ. Cytomegalovirus enteritis among hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2001; **7**: 674-679 [PMID: 11787530 DOI: 10.1053/bbmt.2001.v7.pm11787530]

28 **Torres HA**, Kontoyiannis DP, Bodey GP, Adachi JA, Luna MA, Tarrand JJ, Nogueras GM, Raad II, Chemaly RF. Gastrointestinal cytomegalovirus disease in patients with cancer: a two decade experience in a tertiary care cancer center. *Eur J Cancer* 2005; **41**: 2268-2279 [PMID: 16143517 DOI: 10.1016/j.ejca.2005.07.011]

29 **Cello JP**. AIDS-associated gastrointestinal disease. In: Sande M, Volberding P. The medical management of AIDS. Philadelphia: W. B. Saunders Co., 1990: 145-160

30 **Drew WL**. Nonpulmonary manifestations of cytomegalovirus infection in immunocompromised patients. *Clin Microbiol Rev* 1992; **5**: 204-210 [PMID: 1315617 DOI: 10.1128/CMR.5.2.204]

31 **Hawley DA**, Schaefer JF, Schulz DM, Muller J. Cytomegalovirus encephalitis in acquired immunodeficiency syndrome. *Am J Clin Pathol* 1983; **80**: 874-877 [PMID: 6314804]

32 **Wolf DG**, Lurain NS, Zuckerman T, Hoffman R, Satinger J, Honigman A, Saleh N, Robert ES, Rowe JM, Kra-Oz Z. Emergence of late cytomegalovirus central nervous system disease in hematopoietic stem cell transplant recipients. *Blood* 2003; **101**: 463-465 [PMID: 12393485 DOI: 10.1182/blood-2002-07-1982]

33 **Reddy SM**, Winston DJ, Territo MC, Schiller GJ. CMV central nervous system disease in stem-cell transplant recipients: an increasing complication of drug-resistant CMV infection and protracted immunodeficiency. *Bone Marrow Transplant* 2010; **45**: 979-984 [PMID: 20190836 DOI: 10.1038/bmt.2010.35]

34 **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**: 4063-4071 [PMID: 8916975]

35 **Crippa F**, Corey L, Chuang EL, Sale G, Boeckh M. Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. *Clin Infect Dis* 2001; **32**: 214-219 [PMID: 11170910 DOI: 10.1086/318447]

36 **Danise A**, Cinque P, Vergani S, Candino M, Racca S, De Bona A, Novati R, Castagna A, Lazzarin A. Use of polymerase chain reaction assays of aqueous humor in the differential diagnosis of retinitis in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1997; **24**: 1100-1106 [PMID: 9195064 DOI: 10.1086/513625]

37 **Ljungman P**, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002; **34**: 1094-1097 [PMID: 11914998 DOI: 10.1086/339329]

38 **Preiser W**, Bräuninger S, Schwerdtfeger R, Ayliffe U, Garson JA, Brink NS, Franck S, Doerr HW, Rabenau HF. Evaluation of diagnostic methods for the detection of cytomegalovirus in recipients of allogeneic stem cell transplants. *J Clin Virol* 2001; **20**: 59-70 [PMID: 11163584 DOI: 10.1016/S1386-6532(00)00156-6]

39 **Sanghavi SK**, Abu-Elmagd K, Keightley MC, St George K, Lewandowski K, Boes SS, Bullotta A, Dare R, Lassak M, Husain S, Kwak EJ, Paterson DL, Rinaldo CR. Relationship of cytomegalovirus load assessed by real-time PCR to pp65 antigenemia in organ transplant recipients. *J Clin Virol* 2008; **42**: 335-342 [PMID: 18495527 DOI: 10.1016/j.jcv.2008.03.031.]

40 **Degré M**, Kristiansen KI, Rollag H, Holter E, Nordal KP. Detection of human cytomegalovirus (HCMV) pp67-mRNA and pp65 antigenemia in relation to development of clinical HCMV disease in renal transplant recipients. *Clin Microbiol Infect* 2001; **7**: 254-260 [PMID: 11422252 DOI: 10.1046/j.1198-743x.2001.00251.x]

41 **Berger A**, Braner J, Doerr HW, Weber B. Quantification of viral load: clinical relevance for human immunodeficiency virus, hepatitis B virus and hepatitis C virus infection. *Intervirology* 1998; **41**: 24-34 [PMID: 9705562]

42 **Preiser W**, Elzinger B, Brink NS. Quantitative molecular virology in patient management. *J Clin Pathol* 2000; **53**: 76-83 [PMID: 10767862 DOI: 10.1136/jcp.53.1.76]

43 **Tanaka Y**, Kanda Y, Kami M, Mori S, Hamaki T, Kusumi E, Miyakoshi S, Nannya Y, Chiba S, Arai Y, Mitani K, Hirai H, Mutou Y. Monitoring cytomegalovirus infection by antigenemia assay and two distinct plasma real-time PCR methods after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2002; **30**: 315-319 [PMID: 12209354 DOI: 10.1038/sj.bmt1703661]

44 **Bowden RA**, Slichter SJ, Sayers M, Weisdorf D, Cays M, Schoch G, Banaji M, Haake R, Welk K, Fisher L, McCullough J, Miller W. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. *Blood* 1995; **86**: 3598-3603 [PMID: 7579469]

45 **Tomblyn M**, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JA, Boeckh MJ. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* 2009; **15**: 1143-1238 [PMID: 19747629 DOI: 10.1016/j.bbmt.2009.06.019]

46 **Avery RK**, Adal KA, Longworth DL, Bolwell BJ. A survey of allogeneic bone marrow transplant programs in the United States regarding cytomegalovirus prophylaxis and pre-emptive therapy. *Bone Marrow Transplant* 2000; **26**: 763-767 [PMID: 11042658]

47 **Ljungman P**, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. *Hematol Oncol Clin North Am* 2011; **25**: 151-169 [PMID: 21236396 DOI: 10.1016/j.hoc.2010.11.011]

48 **Reusser P**, Einsele H, Lee J, Volin L, Rovira M, Engelhard D, Finke J, Cordonnier C, Link H, Ljungman P. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood* 2002; **99**: 1159-1164 [PMID: 11830461 DOI: 10.1182/blood.V99.4.1159]

49 **Cesaro S**, Zhou X, Manzardo C, Buonfrate D, Cusinato R, Tridello G, Mengoli C, Palù G, Messina C. Cidofovir for cytomegalovirus reactivation in pediatric patients after hematopoietic stem cell transplantation. *J Clin Virol* 2005; **34**: 129-132 [PMID: 16157264 DOI: 10.1016/j.jcv.2005.02.009]

50 **Ariza-Heredia EJ**, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. *Cancer Lett* 2014; **342**: 1-8 [PMID: 24041869 DOI: 10.1016/j.canlet.2013.09.004]

51 **Ljungman P**, Cordonnier C, Einsele H, Bender-Götze C, Bosi A, Dekker A, De la Camara R, Gmür J, Newland AC, Prentice HG, Robinson AJ, Rovira M, Rösler W, Veil D. Use of intravenous immune globulin in addition to antiviral therapy in the treatment of CMV gastrointestinal disease in allogeneic bone marrow transplant patients: a report from the European Group for Blood and Marrow Transplantation (EBMT). Infectious Diseases Working Party of the EBMT. *Bone Marrow Transplant* 1998; **21**: 473-476 [PMID: 9535039 DOI: 10.1038/sj.bmt.1701113]

52 **Machado CM**, Dulley FL, Boas LS, Castelli JB, Macedo MC, Silva RL, Pallota R, Saboya RS, Pannuti CS. CMV pneumonia in allogeneic BMT recipients undergoing early treatment of pre-emptive ganciclovir therapy. *Bone Marrow Transplant* 2000; **26**: 413-417 [PMID: 10982288]

53 **Marty FM**, Boeckh M. Maribavir and human cytomegalovirus-what happened in the clinical trials and why might the drug have failed? *Curr Opin Virol* 2011; **1**: 555-562 [PMID: 22440913 DOI: 10.1016/j.coviro.2011.10.011]

54 **Feuchtinger T**, Opherk K, Bethge WA, Topp MS, Schuster FR, Weissinger EM, Mohty M, Or R, Maschan M, Schumm M, Hamprecht K, Handgretinger R, Lang P, Einsele H. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. *Blood* 2010; **116**: 4360-4367 [PMID: 20625005 DOI: 10.1182/blood-2010-01-262089]

**P-Reviewer:** Guo Redondo PC **ZK, S-Editor:** Qiu S **L-Editor: E-Editor:**