SUPPLEMENT ARTICLE

Management of Cytomegalovirus Infection and Disease after Solid-Organ Transplantation

Wim van der Bij[1] and Rudolf Speich[2]

[1]Department of Clinical Immunology, University Hospital, Groningen, The Netherlands; and [2]Department of Internal Medicine, University Hospital, Zurich, Switzerland

Cytomegalovirus (CMV) continues to be a cause of substantial morbidity and death after solid-organ transplantation. There are 3 major consequences of CMV infection: CMV disease, including a wide range of clinical illnesses; superinfection with opportunistic pathogens; and injury to the transplanted organ, possibly enhancing chronic rejection. This article discusses the considerable progress that has been made in elucidating risk factors for CMV disease, in the rapid detection of CMV in clinical specimens, and in the use of antiviral chemotherapy and immunoglobulin to prevent and treat CMV disease after solid-organ transplantation.

CLINICAL CONTEXT AND DEFINITIONS

Cytomegalovirus (CMV) is a ubiquitous virus; the seropositivity in the population ranges worldwide from 40% to >90%. Because of its opportunistic behavior under immunosuppression, active CMV infections generally have a large impact on the clinical course of organ transplant recipients. The negative influence of CMV on the results of transplantation is beyond any doubt.

Depending on donor-recipient (D/R) match, diagnostic techniques, and mode and magnitude of immunosuppression, the onset of the majority of active CMV infections after solid-organ transplantation ranges from 2 weeks to several months after transplantation. Active CMV infection occurs in 30%–75% of the transplant recipients at risk, with a mortality rate of ~5%, even at present. Serious and often fatal secondary infections (especially fungal) are of great concern. At greatest risk are patients with a D+/R− match, patients undergoing lympholytic induction or rejection therapy, and patients with previous or concomitant (super-)infections. Whereas the incidence of CMV disease is 8%–35% in kidney, heart, and liver transplant recipients, its frequency is considerably higher in pancreas or kidney-pancreas (50%) and lung or heart-lung transplant recipients (50%–80%).

A number of effects and sequelae have been linked to (active) CMV infection, such as CMV-related symptoms and organ dysfunction; contribution to the so-called net state of immunosuppression after organ transplantation; the clinical observation of a mutual influence between CMV infection and acute transplant rejection; a possible role of CMV in the development of chronic transplant dysfunction, such as accelerated coronary atherosclerosis after heart transplantation, vanishing bile duct syndrome after liver transplantation, and bronchiolitis obliterans syndrome after lung transplantation; and a role as an independent risk factor in the development of posttransplant lymphoproliferative disease.

The following definitions are often used with regard to CMV infection: *latency:* carriership of the CMV genome in a seropositive individual with a primarily low-grade, persistent infection, but without signs of active viral replication; *active infection:* a state of viral replication characterized by the detectable presence of CMV in blood or organs and/or a significant rise in CMV-specific antibodies; *primary infection:* active infection in a previously nonimmune seronegative individual (e.g., in a CMV-seronegative recipient of an organ from a

Reprints or correspondence: Dr. Wim van der Bij, Dept. of Clinical Immunology, University Hospital, Hanzeplein 1, 9713 GZ Groningen, The Netherlands (w.van.der.bij@int.azg.nl).

Clinical Infectious Diseases 2001; 33(Suppl 1):S33–7

1058-4838/2001/3301S1-0007$03.00

seropositive donor); *secondary infection:* active infection in an already seropositive individual (e.g., a reactivation in a CMV-seropositive organ transplant recipient); *CMV disease or syndrome:* clinical expression of active infection, ranging from general discomfort, fever, myalgia, or arthralgia to organ involvement (hepatitis, pneumonitis, gastroenteritis, colitis, encephalitis, and so forth) or a severe, often life-threatening, wasting disease.

Most available information, based on both clinical experience and reports from the literature, is derived from the clinical context of immunosuppression today (i.e., varying combinations of cyclosporine or tacrolimus, azathioprine, prednisolone, antilymphocyte antibody preparations, or OKT3). Nevertheless, since (1) more "rejection-sensitive" types of transplantation are being performed (e.g., lung transplantation) or introduced (e.g., bowel transplantation), (2) chronic transplant dysfunction is still a major impediment to long-term graft and patient survival, and (3) more potent immunosuppressant drugs are becoming available, there will be an inevitable tendency to intensify immunosuppression, with its inherently increased risk of opportunistic infections. This development obviously will influence our considerations and recommendations with regard to diagnosis and therapy of CMV. The practical consequence is that reliable and efficient diagnostic tools and effective therapy will become increasingly important. Intensification of antimicrobial, especially prophylactic, measures will also be a logical consequence.

The goal of CMV management is to prevent or to treat CMV disease with a minimum of side effects. On the basis of the differential susceptibility of the respective organ transplants to rejection and infection, groupings of transplants into low risk (kidney), intermediate risk (liver, heart, pancreas), and high risk (lung, intestine, bone marrow) for CMV infection may be used arbitrarily. Apart from the type of transplant, certain clinical states of increased immunosuppression (e.g., during the administration of lympholytic therapy or intensified maintenance immunosuppression) will add to the "a priori" risk of serious CMV infection. Efficacy and toxicity of antiviral measures should be proportional to this risk.

Thus, major determinants for the management of CMV are the type of organ transplantation, the type and extent of immunosuppression, the possibility and/or necessity of seromatching, the availability of tools for rapid and early diagnosis and monitoring, and the qualities of the antiviral compounds.

DIAGNOSIS

Determination of the CMV serostatus of donor and recipient is important in anticipation of the type and thus the clinical risk of active CMV infection. CMV-DNA [1] and CMV-RNA [2] could be demonstrated in >25% of seronegative blood donors. This underscores that a sensitive serological technique is mandatory for determination of the CMV serostatus, mainly to prevent misjudgment of seropositivity of the donor (false seronegativity).

On the other hand, misjudgment of the seronegative donor (false seropositivity) may lead to erroneous risk stratification after transplantation. Techniques such as ELISA, radioimmunoassay, or indirect hemagglutination assay [3–5] are superior to obsolete tests such as complement fixation test or passive hemagglutination assay.

Recommendation: Efficient and sensitive serological assays (preferably ELISA or indirect hemagglutination assay) should be used to determine the serostatus of donor and recipient (A-II).

Serological techniques are of limited value for the diagnosis of active infection after transplantation, and certainly during increased intensity of immunosuppression. Significant antibody rises simply come (too) late, and tests for IgM often remain negative. Those patients showing increases of CMV-specific antibody without viremia, antigenemia, DNAemia, or tissue invasion represent the mildest cases.

CMV viruria is a classical marker of CMV infection but may be present for years. For this reason, it is not the diagnostic measure of choice for most centers. In one report [6], however, quantitation of viral DNA in urine by quantitative PCR (qPCR) showed a correlation between virus load and the clinical expression of disease.

Clinically relevant CMV infection after organ transplantation is associated with viremia [7] and/or organ infiltration. For this reason, active CMV infection is most efficiently diagnosed and followed by a technique that allows rapid, early, sensitive, and specific determination of the presence of the virus or virus products in blood or the organ in question. Culture and rapid shell vial assay methods of detecting CMV [8] are generally less sensitive, more elaborative, and more time-consuming than are methods to detect CMV, antigenemia, or viral nucleic acids in blood (preferentially by qPCR) and immunohistochemical techniques, which were developed and introduced during the 1990s.

Detection of CMV-pp65 in peripheral blood leukocytes (antigenemia) has proved to be superior to tests based on virus isolation [9–11]. The test is applicable in all transplant recipients. In CMV disease, antigenemia runs parallel with the period of symptoms. An additional advantage is the possibility to quantify the virus load and the subsequent link to preemptive therapy [12]. Varying thresholds (10/50,000–100/200,000 positive circulating peripheral blood leukocytes) for therapeutic intervention have been suggested. Standardization of the technique is needed [13], because of interlaboratory variation with respect to assay sensitivity.

DNA hybridization and, especially, PCR [14–16] are now being implemented for early detection of DNA/RNAemia and thus the diagnosis of active infection after transplantation. These assays generally have a sensitivity and specificity for the diagnosis of active infection of >80% and diagnose active infection 1–3 weeks before conventional tools or CMV disease.

From a practical and technical point of view, there is considerable variation between laboratories in choice of blood components, primers, and amplification schemes. For instance, the buffy coat fraction (mainly the polymorphonuclear cells) is reported to carry the highest copy numbers. The mononuclear cell fraction remains positive long after treatment and is frequently positive during latency [17]; however, an earlier study [15] suggested that PCR of plasma samples after bone marrow or kidney transplantation may prove useful in diagnosis and therapy guidance. A report [18] on PCR primers for the detection of CMV-DNAemia suggested that a primer directed to the *Hin*dIII-X region was clinically useful for early diagnosis (sensitivity 100% for symptomatic disease, but specificity disappointingly low at 45%).

Comparative studies of CMV antigenemia detection versus PCR for DNAemia [19–24] in a variety of organ transplantations permit the following conclusions. Both assays have a concordancy of ⩾80%. Both assays are superior to other tests with respect to early diagnosis (PCR slightly earlier than antigenemia), frequently (in >80% of cases) detecting CMV 0–2 weeks before onset of disease. Because of the possibility of enumeration of CMV-pp65 cells, it seems that, with respect to monitoring of active infection and clinical disease, antigenemia detection is superior to the classical PCR. Further development of qPCR will probably equalize this difference. A final difference between both assays is technical in nature: although CMV antigenemia detection is probably less demanding than PCR, the latter can be implemented in the array of routine PCRs. Intercenter quality control and standardization are relevant for both assays.

Recommendation: Detection tests for CMV antigenemia or DNA/RNAemia (especially qPCR) are methods of choice for diagnosis and monitoring of active CMV infection after organ transplantation (A-II).

SURVEILLANCE

Surveillance is a prerequisite for preemptive treatment, based on laboratory parameters, for those patients at increased risk of CMV disease. CMV antigenemia testing or qPCR is useful for surveillance of active infection (A-II). In some centers, however, virus detection in urine samples is also advocated for surveillance [25].

PREVENTION

A number of studies have demonstrated effects of vaccination of volunteers and hemodialysis patients with CMV. In one such study, live, attenuated Towne strain of CMV was administered to CMV-seronegative patients on hemodialysis. In case of transplantation of a kidney from a seropositive donor, the incidence of primary infection was not influenced, but the infection showed a more benign clinical course [26]. Active immunization, however, has not reached broad clinical application. Avoidance of primary infection, whenever possible, is preferred, because this type of infection is the most harmful for the transplant recipient in terms of morbidity and death. The logical approach is to match seronegative donors to seronegative recipients with respect to both the transplanted organ and the use of blood and blood components; however, the CMV-induced morbidity and mortality rates should be weighed against the degree of donor shortage in the respective organ transplantation.

Recommendation: Seromatching for CMV is strongly advised in cases of lung and intestinal transplantation (A-II).

TREATMENT

Types of treatment are the following [27]: *therapeutic use:* treatment based on the presence of established infection; *prophylactic use:* use of antimicrobial therapy from the earliest possible moment; *preemptive use:* antimicrobial therapy before clinical signs of infection, guided by a clinical or epidemiological characteristic or a prospective surveillance technique; *deferred therapy:* initiation of therapy after onset of disease, guided by a fixed laboratory or other marker.

ANTIVIRAL THERAPY (OF ESTABLISHED DISEASE)

Therapy with ganciclovir (Gcv) was implemented at a time when therapy was desperately needed, without formal randomized, controlled studies. In therapeutic use in the classical sense (i.e., at the onset of clinical disease), iv Gcv is the cornerstone of therapy. Anti-CMV hyperimmunoglobulin preparations are useful adjuncts in seronegative recipients of seropositive organs; foscarnet can be considered as rescue therapy (because of its inherent toxicity) in case of Gcv failure.

Recommendation: In the therapeutic setting of CMV disease, iv Gcv is the drug of choice. In the case of clinical nonresponsiveness or signs of Gcv resistance, a switch to foscarnet is advised (A-II).

ANTIVIRAL PROPHYLAXIS

Studies on anti-CMV prophylaxis show a large variety in many aspects: type of transplantation or subgroup within that par-

ticular transplantation, type or combination of compounds, study setup, and end points.

Anti-CMV Hyperimmunoglobulins

Randomized, placebo-controlled trials to determine the efficacy of anti-CMV hyperimmunoglobulin preparations have been conducted in the setting of liver [28, 29] and kidney transplantation [30]. Taken together, this prophylaxis significantly lowered the rate of (severe) CMV disease (A-I). Except for patients with a D+/R− match, the risk of CMV disease was significantly lower even after OKT3 treatment [29]. A smaller placebo-controlled study of kidney transplantation [31] showed an effect of anti-CMV hyperimmunoglobulin in patients with a D+/R− match only after administration of lympholytic rejection therapy (B-II). With regard to passive immunization with anti-CMV hyperimmunoglobulin preparations, it is not known which CMV antigen(s) and, consequently, which CMV-specific antibodies are immunorelevant. Because it is a biological product, product-to-product and also batch-to-batch variations are to be expected. The product is expensive, although probably cost-effective [32].

Gcv

The prophylactic application of Gcv is the main focus of a growing number of studies. In a concise meta-analysis of a number of randomized, controlled trials (A-I) [33], iv or oral Gcv or high-dose oral acyclovir (Acy) was compared with placebo or no treatment on the occurrence of CMV infection or disease in patients after solid-organ (kidney, heart, or liver) transplantation. Prophylactic treatment with either Gcv or Acy in both kidney and liver transplant recipients resulted in significant risk reduction for CMV infection and disease. For heart transplant recipients (donor or recipient seropositive), a significant reduction of disease was also calculated. Subgroup analysis showed that Gcv significantly reduced both the rate of infection and disease, whereas Acy affected the rate of disease. Consequently, despite the lack of viral thymidine kinase activity, Acy is effective in vivo.

Kidney transplantation. In a prospective, randomized, controlled study, 44 kidney transplant recipients received either oral Gcv, 750 mg b.i.d. for 3 months postoperatively, or no prophylaxis [34]. CMV infection occurred in 1 patient (5%) in the Gcv group and 6 patients (27%) in the control group ($P < .05$), whereas the frequency of biopsy-proven allograft rejections were 5% (1 of 21) and 18% (4 of 22), respectively. Only 1 of these patients developed CMV disease.

Another prospective randomized, controlled trial was carried out in 42 kidney transplant recipients who were followed for 6 months after transplantation [35]. Prophylaxis with oral Gcv (1000 mg t.i.d.), given during the first 12 postoperative weeks, was compared with oral Acy (200 mg b.i.d.), followed by deferred therapy based on PCR results. No patients in the Gcv group, compared with 14 of 23 patients (61%) in the deferred-therapy group, developed CMV disease during the first 12 weeks ($P < .0001$). Moreover, beyond the first 3 months, the patients in the Gcv group experienced a significantly lower frequency and later onset of CMV disease and viremia than did the deferred-therapy group. The authors concluded that an initial 12-week course of oral Gcv prevents CMV disease and infection in kidney transplant recipients during prophylaxis, and the benefits persist after discontinuation (A-I).

Liver transplantation. The efficacy of antiviral prophylaxis with oral Gcv the first 3 months after transplantation was investigated in a prospective randomized study of 304 liver transplant recipients [36]. Oral Gcv significantly influenced the 6-month incidence of CMV disease (4.8% vs. 18.9% in the placebo arm), even in patients with a D+/R− match, and even in those patients receiving lympholytic treatment (A-I).

Heart transplantation. A large randomized, double-blind, placebo-controlled trial has been conducted in 149 heart transplant recipients [37]. Intravenous Gcv (5 mg/kg b.i.d.) was given from postoperative day 1 through day 14, then at a dose of 6 mg/kg daily for 5 days per week until day 28. CMV disease occurred in 26 of 56 (46%) seropositive patients given placebo, as compared with 5 of 56 (9%) patients treated with Gcv ($P < .001$). Whereas more of the Gcv-treated patients had mild, transient elevation of serum creatinine concentrations (18% vs. 4%), the incidence of neutropenia was similar in both groups. One patient in the Gcv group died of sepsis, but the authors did not mention whether there were any catheter-related problems (A-I).

Lung transplantation. In one of the earlier lung transplant studies on CMV prophylaxis, 25 allograft recipients received Gcv during the first 3 postoperative weeks and were then randomized to either Gcv, 5 mg/kg daily 5 days/week, or Acy, 800 mg q.i.d. until day 90 [38]. Compared with the Acy group, the cumulative incidence of all CMV infections in the Gcv group was lower (15% vs. 75%; $P < .01$), as was the incidence of organ manifestations (overt CMV shedding and/or pneumonitis) (15% vs. 50%; $P < .043$). Moreover, it seemed that the risk of obliterative bronchiolitis during the first year after transplantation was lower in the Gcv group (17% vs. 54%; $P < .033$). Use of intravenous catheters for Gcv administration resulted in 4 complications among 3 patients of the Gcv group (23%) (A-I).

The efficacy, tolerance, and cost-effectiveness of Gcv prophylaxis after lung transplantation were evaluated in an open, comparative study in 22 patients [39]. Intravenous Gcv (5 mg/kg b.i.d. for 14 days), followed by either iv Gcv (5 mg/kg daily; $n = 5$) or oral Gcv (1000 mg t.i.d.; $n = 9$), was given up to 90 days. Thereafter, oral Gcv was continued until prednisone was tapered below 15 mg/day. Prophylaxed groups were compared with a historical control ($n = 8$) with respect to CMV

Table 1. Management of cytomegalovirus (CMV) infection, according to type of solid-organ transplantation and established risk factors.

	Kidney transplant		Liver/heart/pancreas transplant		Lung/bowel transplant	
	No ALA	ALA used	No ALA	ALA used	No ALA	ALA used
R+	1	2	3 (or 2)	3 (or 2)	3	3
D+/R−	3 (or 2)	3 (or 2)	3	3	3, 4	3, 4

NOTE. ALA, antilymphocytic antibodies; Gcv, ganciclovir; qPCR, quantitative polymerase chain reaction; R+, recipient seropositive for CMV; D+/R−, donor seropositive and recipient seronegative for CMV; 1, treatment with iv Gcv in case of CMV disease, given for 2–3 weeks or until results of a surveillance technique such as tests for antigenemia or qPCR are repeatedly negative; 2, preemptive use of iv Gcv, given for 2–3 weeks or until results of a surveillance technique such as tests for antigenemia or qPCR are repeatedly negative, or while ALA is administered; 3, prophylaxis with oral Gcv (1000 mg t.i.d.) during the first 3 months after transplantation (3 months is chosen on the basis of data from the literature and the fact that the risk of acute rejection generally decreases after 3 months); 4, anti-CMV hyperimmunoglobulins. In case of CMV relapse after cessation of antiviral therapy, Gcv should be reinstituted in accordance with hospital practice. Foscarnet should be administered if the patient does not respond to Gcv.

disease, in-hospital stay, overall costs, and survival. Follow-up times and the net state of immunosuppressive therapy between groups were comparable. Six (75%) of the nonprophylaxed patients developed CMV disease, compared with 0 in the iv and 1 in the oral Gcv group ($P = .013$). The nonprophylaxed patients had a longer CMV-related in-hospital stay ($P = .018$) and insignificantly higher CMV-related costs. Bronchiolitis obliterans syndrome was less frequent with prophylaxis ($P = .039$), and the survival rate tended to be higher ($P = .072$). The only adverse effect was a subclavian vein thrombosis in the iv Gcv group (A-II).

PREEMPTIVE TREATMENT

In 2 studies, the efficacy of preemptive Gcv therapy after kidney transplantation was evaluated [40, 41]. Intravenous Gcv (vs. no antiviral therapy), given during the period of treatment with antilymphocyte antibodies, was shown to significantly reduce the rate of CMV disease (from 33% to 14%) and viremia (from 35% to 17%) (A-I).

With use of detection of CMV antigenemia with a predefined level of 50 CMV-pp65-positive polymorphonuclear leukocytes/2×10^5 polymorphonuclear leukocytes as the surveillance tool, iv Gcv (10 mg/kg/day) prevented CMV disease in 19 heart or lung transplant recipients, as compared with 5 cases of CMV disease in 18 historic controls [42]. The onset of high-level antigenemia in the latter group, however, was 2 weeks earlier (B-II).

SUMMARY OF RECOMMENDATIONS

A scheme for CMV management after organ transplantation—stratified according to established risk factors (see above) and based on or extrapolated from published data—was elaborated by the consensus panel (categories A-I and A-II, respectively). The results are shown in table 1.

References

1. Larsson S, Soderberg-Naucler C, Wang FZ, Moller E. Cytomegalovirus DNA can be detected in peripheral blood mononuclear cells from all seropositive and most seronegative healthy blood donors over time. Transfusion **1998**; 38:271–8.
2. Zhang LJ, Hanff P, Rutherford C, Churchill WH, Crumpacker CS. Detection of human cytomegalovirus DNA, RNA, and antibody in normal donor blood. J Infect Dis **1995**; 171:1002–6.
3. Booth JC, Hannington G, Bakir TM, et al. Comparison of enzyme-linked immunosorbent assay, radioimmunoassay, complement fixation, anticomplement immunofluorescence and passive haemagglutination techniques for detecting cytomegalovirus IgG antibody. J Clin Pathol **1982**; 35:1345–8.
4. Middeldorp JM, Jongsma J, ter Haar A, Schirm J, The TH. Detection of immunoglobulin M and G antibodies against cytomegalovirus early and late antigens by enzyme-linked immunosorbent assay. J Clin Microbiol **1984**; 20:763–71.
5. Grint PC, Ronalds CJ, Kangro HO, et al. Screening tests for antibodies to cytomegalovirus: an evaluation of five commercial products. J Clin Pathol **1985**; 38:1059–64.
6. Fox JC, Kidd IM, Griffiths PD, Sweny P, Emery VC. Longitudinal analysis of cytomegalovirus load in renal transplant recipients using a quantitative polymerase chain reaction: correlation with disease. J Gen Virol **1995**; 76:309–19.
7. Richardson WP, Colvin RB, Cheeseman SH, et al. Glomerulopathy associated with cytomegalovirus viremia in renal allografts. N Engl J Med **1981**; 305:57–63.
8. Griffiths PD, Panjwani DD, Stirk PR, et al. Rapid diagnosis of cytomegalovirus infection in immunocompromised patients by detection of early antigen fluorescent foci. Lancet **1984**; 2:1242–5.
9. van der Bij W, Torensma R, van Son WJ, et al. Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leucocytes. J Med Virol **1988**; 25:179–88.
10. van den Berg AP, van der Bij W, van Son WJ, et al. Cytomegalovirus antigenemia as a useful marker of symptomatic cytomegalovirus infection after renal transplantation: a report of 130 consecutive patients. Transplantation **1989**; 48:991–5.
11. Bein G, Bitsch A, Hoyer J, et al. A longitudinal prospective study of

cytomegalovirus pp65 antigenemia in renal transplant recipients. Transpl Int **1993**; 6:185–90.
12. Murray BM, Amsterdam D, Gray V, Myers J, Gerbasi J, Venuto R. Monitoring and diagnosis of cytomegalovirus infection in renal transplantation. J Am Soc Nephrol **1997**; 8:1448–57.
13. The TH, van den Berg AP, Harmsen MC, van der Bij W, van Son WJ. The cytomegalovirus antigenemia assay: a plea for standardization. Scand J Infect Dis Suppl **1995**; 99:25–9.
14. Jiwa NM, Van Gemert GW, Raap AK, et al. Rapid detection of human cytomegalovirus DNA in peripheral blood leukocytes of viremic transplant recipients by the polymerase chain reaction. Transplantation **1989**; 48:72–6.
15. Wolf DG, Spector SA. Early diagnosis of human cytomegalovirus disease in transplant recipients by DNA amplification in plasma. Transplantation **1993**; 56:330–4.
16. Kidd IM, Fox JC, Pillay D, Charman H, Griffiths PD, Emery VC. Provision of prognostic information in immunocompromised patients by routine application of the polymerase chain reaction for cytomegalovirus. Transplantation **1993**; 56:867–71.
17. Schafer P, Tenschert W, Cremaschi L, Gutensohn K, Laufs R. Utility of major leukocyte subpopulations for monitoring secondary cytomegalovirus infections in renal-allograft recipients by PCR. J Clin Microbiol **1998**; 36:1008–14.
18. Mendez JC, Espy MJ, Smith TF, Wilson JA, Paya CV. Evaluation of PCR primers for early diagnosis of cytomegalovirus infection following liver transplantation. J Clin Microbiol **1998**; 36:526–30.
19. van Dorp WT, Vlieger A, Jiwa NM, et al. The polymerase chain reaction, a sensitive and rapid technique for detecting cytomegalovirus infection after renal transplantation. Transplantation **1992**; 54:661–4.
20. Schmidt CA, Oettle H, Peng R, et al. Comparison of polymerase chain reaction from plasma and buffy coat with antigen detection and occurrence of immunoglobulin M for the demonstration of cytomegalovirus infection after liver transplantation. Transplantation **1995**; 59: 1133–8.
21. Eriksson BM, Wirgart BZ, Claesson K, et al. A prospective study of rapid methods of detecting cytomegalovirus in the blood of renal transplant recipients in relation to patient and graft survival. Clin Transplant **1996**; 10:494–502.
22. Tanabe K, Tokumoto T, Ishikawa N, et al. Comparative study of cytomegalovirus (CMV) antigenemia assay, polymerase chain reaction, serology, and shell vial assay in the early diagnosis and monitoring of CMV infection after renal transplantation. Transplantation **1997**; 64: 1721–5.
23. Gaeta A, Nazzari C, Angeletti S, Lazzarini M, Mazzei E, Mancini C. Monitoring for cytomegalovirus infection in organ transplant recipients: analysis of pp65 antigen, DNA and late mRNA in peripheral blood leukocytes. J Med Virol **1997**; 53:189–95.
24. Lo CY, Ho KN, Yuen KY, et al. Diagnosing cytomegalovirus disease in CMV seropositive renal allograft recipients: a comparison between the detection of CMV DNAemia by polymerase chain reaction and antigenemia by CMV pp65 assay. Clin Transplant **1997**; 11:286–93.
25. Lao WC, Lee D, Burroughs AK, et al. Use of polymerase chain reaction to provide prognostic information on human cytomegalovirus disease after liver transplantation. J Med Virol **1997**; 51:152–8.
26. Plotkin SA, Starr SE, Friedman HM, et al. Effect of Towne live virus vaccine on cytomegalovirus disease after renal transplant: a controlled trial. Ann Intern Med **1991**; 114:525–31.
27. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med **1998**; 338:1741–51.
28. Falagas ME, Snydman DR, Ruthazer R, et al. Cytomegalovirus immune globulin (CMVIG) prophylaxis is associated with increased survival after orthotopic liver transplantation. The Boston Center for Liver Transplantation CMVIG Study Group. Clin Transplant **1997**; 11:432–7.
29. Snydman DR, Werner BG, Dougherty NN, et al. Cytomegalovirus immune globulin prophylaxis in liver transplantation: a randomized, double-blind, placebo-controlled trial. The Boston Center for Liver Transplantation CMVIG Study Group. Ann Intern Med **1993**; 119:984–91.
30. Snydman DR, Werner BG, Heinze Lacey B, et al. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal-transplant recipients. N Engl J Med **1987**; 317:1049–54.
31. Metselaar HJ, Rothbarth PH, Brouwer RM, Wenting GJ, Jeekel J, Weimar W. Prevention of cytomegalovirus-related death by passive immunization: a double-blind placebo-controlled study in kidney transplant recipients treated for rejection. Transplantation **1989**; 48:264–6.
32. Tsevat J, Snydman DR, Pauker SG, Durand-Zaleski I, Werner BG, Levey AS. Which renal transplant patients should receive cytomegalovirus immune globulin? A cost-effectiveness analysis. Transplantation **1991**; 52: 259–65.
33. Couchoud C, Cucherat M, Haugh M, Pouteil-Noble C. Cytomegalovirus prophylaxis with antiviral agents in solid organ transplantation: a meta-analysis. Transplantation **1998**; 65:641–7.
34. Ahsan N, Holman MJ, Yang HC. Efficacy of oral ganciclovir in prevention of cytomegalovirus infection in post-kidney transplant patients. Clin Transplant **1997**; 11:633–9.
35. Brennan DC, Garlock KA, Singer GG, et al. Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients. Transplantation **1997**; 64:1843–6.
36. Gane E, Saliba F, Valdecasas GJC, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. Lancet **1997**; 350:1729–33.
37. Merigan TC, Renlund DG, Keay S, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med **1992**; 326:1182–6.
38. Duncan SR, Grgurich WF, Iacono AT, et al. A comparison of ganciclovir and acyclovir to prevent cytomegalovirus after lung transplantation. Am J Respir Crit Care Med **1994**; 150:146–52.
39. Speich R, Thurnheer R, Gaspert A, Weder W, Boehler A. Efficacy and cost effectiveness of oral ganciclovir in the prevention of cytomegalovirus disease after lung transplantation. Transplantation **1999**; 67: 315–20.
40. Conti DJ, Freed BM, Singh TP, Gallichio M, Gruber SA, Lempert N. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplants recipients. Arch Surg **1995**; 130:1217–21.
41. Hibberd PL, Tolkoff Rubin NE, Conti D, et al. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. Ann Intern Med **1995**; 123:18–26.
42. Egan JJ, Lomax J, Barber L, et al. Preemptive treatment for the prevention of cytomegalovirus disease: in lung and heart transplant recipients. Transplantation **1998**; 65:747–52.