

# Treatment of Cytomegalovirus disease in renal transplant recipients

**Date written:** February 2010

**Final submission:** August 2011

**Author:** David Goodman

## GUIDELINES

**No recommendations possible based on Level I or II evidence**

## SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- We suggest ganciclovir by IV administration be the treatment of choice for moderate-severe Cytomegalovirus (CMV) disease and patients with gastrointestinal involvement where drug absorption may be impaired.
- Mild CMV disease in adults may be treated with either oral valganciclovir or IV ganciclovir (Level II evidence, single study).
- Drug dose should be reduced in patients with renal impairment.
- Consider reduction in immunosuppressive therapy.
- We suggest graft function be monitored closely as acute rejection may occur.
- Ganciclovir and valganciclovir may cause leukopaenia and increase serum creatinine.
- We suggest treatment should continue for 2-3 weeks or until CMV-DNA is not detectable (Level III evidence).
- Persistence of CMV-DNA after 21 days is associated with disease recurrence.
- Treatment failure may be due to inadequate treatment, super-infection or ganciclovir resistance (Level III evidence).
- Foscarnet and cidofovir remain second-line agents (Level III evidence).

## IMPLEMENTATION AND AUDIT

No recommendations.

## BACKGROUND

Cytomegalovirus disease is characterised by clinical symptoms and signs of disease coupled with microbiological evidence of CMV infection. Disease occurs in 8% of renal transplant recipients compared with liver or combined kidney-pancreas (29%) and heart-lung (39%) recipients. A large proportion of patients have CMV infection detected by blood testing such as PCR or CMV serology without any clinical symptoms or signs of disease.

Patients at greatest risk of developing disease include D+/R– recipients and those who have been given methyl-prednisolone or anti-lymphocyte antibody (ATGAM, ATG, OKT3, and Thymoglobulin®). The diagnosis may be complicated by the fact that CMV infection is frequently associated with super-infection with other bacteria, fungi, protozoa and viruses. The objective of this guideline is to evaluate the currently available studies relating to the treatment of CMV infection in kidney transplant recipients and provide clinical guidelines and/or recommendations, for the treatment of CMV disease, to assist clinicians involved in the care of renal transplant recipients.

## **SEARCH STRATEGY**

**Databases searched:** MeSH terms and text words for CMV were combined with MeSH terms and text words for solid organ transplantation, including kidney transplantation, then combined with MeSH terms and text words for interventions for CMV and combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (July 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search/es:** 14 July 2009.

## **WHAT IS THE EVIDENCE?**

There is only one randomised controlled trial (RCT) for treatment of CMV disease which is a non-inferiority study comparing IV ganciclovir with oral valganciclovir [1]. In addition, 12 month follow up of the initial study cohort has been recently published [2].

### ***Which patients are at greatest risk of CMV disease?***

While many patients will have evidence of CMV infection following transplantation, Sagedal et al (2000) identified donor positive- and recipient-negative CMV status and acute rejection episodes as significant risk factors associated with the development of CMV disease [3].

A total of 477 consecutive renal transplant recipients (397 first transplants and 80 re-transplants) operated on between October 1994 and July 1997 were included in the study. The patients were followed prospectively for 3 months with serial measurements of CMV pp65 antigen being made to detect CMV infection. The incidence of CMV infections in first transplants was 68% in D+/R– and D+/R+ serostatus groups, whereas the incidence of CMV disease was higher in D+/R– (56%) than in D+/R+ patients (20%,  $P < 0.001$ ).

No difference in severity of CMV disease in D+/R– and D+/R+ was seen except for an increased incidence of hepatitis in primary infections. Cox regression analysis showed that rejection (RR 2.5,  $P < 0.01$ ) and serostatus group D+/R– (RR 3.9,  $P < 0.001$ ) were significant risk factors for the development of CMV disease.

### ***Intravenous ganciclovir***

There are over 30 uncontrolled, non-randomised studies using ganciclovir to treat CMV disease. The study by Rondeau et al was one of the first reported and recommended

ganciclovir dose reductions in patients with renal impairment [4]. In this study, 32 renal transplant recipients with proven CMV disease were treated with ganciclovir for 14 days. The mean time to CMV disease was 49 days. Twenty-nine patients, 10 of whom had moderate to severe disease were improved with treatment. Three deaths occurred, with 2 dying from combined severe pulmonary and hepatic CMV disease. Adverse effects of ganciclovir therapy included leukopaenia (n = 7), thrombocytopenia (n = 2) and abdominal pain (n = 1). Cytomegalovirus was no longer found in virological samples from 80.0% of patients. The clearance of ganciclovir was linearly correlated with creatinine clearance.

### **Oral ganciclovir**

The inconvenience associated with the administration of IV ganciclovir, requiring hospitalisation and frequent intravenous cannulation, has led to a search for effective oral therapy. Jordan et al describe a small study using oral ganciclovir for the treatment of moderate CMV disease using quantitative PCR to monitor treatment [5]. Fifteen patients with donor/recipient CMV status of D+/R– (53%), D+/R+ (40%) and D–/R+ (7%) were studied. All patients were commenced on oral ganciclovir 1g t.i.d. with dose reduction in patients with impaired renal function. Treatment continued until the CMV-PCR copy number was negative and symptoms resolved. The mean number of CMV copies at the time of diagnosis was 580 (normal < 5) and fell to 65 copies after 5-7 days of treatment. A total of 14/15 patients responded to treatment and 1 non-responder was attributed to non-compliance. While the time to disease onset following transplantation is not indicated in the report, it can be inferred from the prophylactic protocol for D+/R– patients (comprising 1 week IV ganciclovir followed by 4 months of oral ganciclovir therapy) that CMV disease occurred more than 4 months after transplantation.

### **Oral valganciclovir**

The development of valganciclovir resulted in a 10-fold increase in oral bioavailability. Pescovitz et al (1999) compared valganciclovir at a dose of 900 mg, twice daily for 21 days, with IV ganciclovir in 28 healthy liver transplant recipients, using a 4-way randomised cross-over design [6]. After 21 days, all patients received oral valganciclovir 900 mg daily until day 50. The AUC for IV ganciclovir was 47.61 mg/h/mL compared with 42.69 for valganciclovir. Thus, valganciclovir achieved 90% (90% CI: 83-97) of IV ganciclovir AUC in transplant recipients but it remains to be proven that valganciclovir absorption is maintained in sick patients with CMV disease.

Humar et al (2005) studied 32 patients with CMV (23 with symptomatic disease) who received valganciclovir for a minimum of 2 weeks and were compared with matched historic controls treated with IV ganciclovir [7]. Kidney transplants including kidney-pancreas accounted for 40% of each group. Matching of controls included type of transplant and viral load. Eligibility for enrolment was at the discretion of the treating physician. Patients with “life-threatening” disease, severe diarrhoea or mucositis were excluded from the study. Clearance of viraemia by day 21 and change in viral load by days 7 and 14 were similar in both groups. Clinical success was 100% in the IV group compared with 93.8% in the valganciclovir group due to 2 patients who failed to respond to oral therapy and were switched to IV ganciclovir.

Asberg et al reported a company-sponsored (VICTOR study) randomized study of 321 adults who received solid organ transplants, of which 73.8% were kidney transplants.

Study patients had both virological and clinical evidence of CMV disease. Those with “life threatening” (severe) disease and/or CrCl < 10 mL/min were excluded from the study. The majority of patients had received previous anti-CMV therapy before developing CMV disease. Patients were randomized to receive either 900 mg valganciclovir daily or 5 mg/kg ganciclovir for 21 days, followed by 900 mg daily valganciclovir. The success rate for viraemia eradication at day 21 was 45.1% for valganciclovir and 48.4% for ganciclovir and at day 49, 67.1% vs 70.1%. Treatment success was 77.4% vs 80.3%, at day 49. Viral loads were not different between the groups and reduced at similar rates following initiation of treatment. Side effects and discontinuations were similar in both groups. The study concluded that oral valganciclovir was non-inferior to IV ganciclovir for the patients studied. One concern with the study is that to demonstrate non-inferiority ( $P < 0.05$ ) each study arm must include 159 patients. The IV ganciclovir arm only recruited 157 patients.

One year follow up of the VICTOR study showed a clinical recurrence rate beyond day 49 of 15.1% with no difference between study arms [2]. Virological recurrence was 30% and again was not different between study arms. Multivariable logistic regression analysis found that failure to eradicate DNAemia by day 21 was a significant predictor of CMV recurrence (OR clinical 3.9 and virological 5.6). Ganciclovir resistance was identified in 8 patients. Twenty patient deaths were recorded, 12 due to infections, of which two involved CMV. This study added additional support to the initial study which found that oral valganciclovir was non-inferior to IV ganciclovir for the patients studied.

The Spanish Network for Research on Infection in Transplantation collected data prospectively on 3476 solid organ transplant recipients, of which ~50% were renal transplants [8]. Cytomegalovirus positive donors to CMV negative recipients (except lung) were given prophylactic ganciclovir 5 mg/kg daily. Patients were switched as soon as possible to either ganciclovir (3 g/d) or valganciclovir (900 mg/d) for the first 100 days post-transplant. Weekly blood testing was performed in recipients who did not receive prophylaxis or when prophylactic treatment was completed. A total of 376 episodes of CMV pre-emptive therapy or disease were recorded and treated with either IV ganciclovir or valganciclovir. In asymptomatic patients and those with CMV viral syndrome, there was no difference in treatment outcome between the two groups. There were fewer patients with focal/ tissue invasive disease in the valganciclovir group (7%) compared with those treated with IV ganciclovir (21% & 32%) presumably due to physician selection bias.

### ***Disease recurrence***

One measure of treatment efficacy is the prevalence of recurrent CMV disease following standard IV ganciclovir therapy. Sawyer et al address this issue in both kidney and combined kidney-pancreas recipients [9].

A total of 619 transplant recipients (535 kidney [253 living related and 282 cadaveric donors] and 84 combined cadaveric kidney-pancreas transplants) were studied over a 3.5-year period. Of these, 114 (18.4%) developed tissue-invasive CMV disease and were treated with IV ganciclovir for 14 to 21 days. Twenty-eight (24.6%) developed recurrent CMV disease after more than 30 days from first infection. Proportionally, more kidney-pancreas transplants than kidney transplant alone relapsed. All patients with recurrent disease were re-treated with IV ganciclovir, achieving a cure rate of 100% at 30 days.

With the introduction of molecular markers of disease activity, Sia et al (2000) followed CMV-DNA load prospectively in patients with CMV infection and disease and

demonstrated that DNA load is predictive of CMV relapse following transplantation [10]. Twenty-four solid-organ transplant recipients (heart, liver, and kidney) with CMV infection (42%) or disease (58%) were tested for CMV-DNA load beforehand and after 14 days of IV ganciclovir therapy. Recurrent infection or disease occurred in 8/24 (33%) patients, with no significant difference between CMV infected and CMV disease groups. The median pre-treatment viral loads were higher in the relapsing group than in the cured group. Most importantly, the relapsing group had detectable CMV-DNA after treatment, whereas the CMV-DNA was undetectable in the non-relapsing patients.

Primary gastrointestinal CMV following transplantation may behave differently to non-gastrointestinal related disease as suggested by Eida et al (2010) [11]. Twenty-six transplant recipients, of whom half had received a kidney transplant, had biopsy-proven evidence of CMV in the gastrointestinal tract. Twenty-five patients were treated initially with IV ganciclovir for 34 days followed by oral valganciclovir. The median time to CMV PCR negativity in blood was 22.5 days. Cytomegalovirus relapse occurred in 27% of patients and correlated with extensive gastrointestinal disease and not to viral load, treatment duration or endoscopic findings at the end of therapy.

### **Superinfection**

Patients with CMV disease are at risk of superinfection with a variety of microorganisms. *Pneumocystis carinii* pneumonia (PCP) in the early post-transplant period contributes significantly to early transplant morbidity and mortality. The link between CMV disease, allograft rejection episodes and PCP is not clearly defined. Arend et al attempt to link these in a small study of 15 renal transplant recipients with proven PCP compared with 95 control patients [12]. The number of rejection episodes correlated with increased risk of developing PCP. After 1, 2 or 3 rejection episodes, the relative risk of developing PCP increased to 1.7 (95% CI: 0.2-12.5), 4.8 (95% CI: 0.9-25.5), and 9.5 (95% CI: 1.6-56.4), respectively. Furthermore, CMV infection increased the relative risk of PCP five-fold (95% CI: 1.6-15.8) with the highest relative risk of 5.7 in the D+R- combination (95% CI: 1.4-22.3).

### **Ganciclovir resistance**

Inadequate clinical response to antiviral therapy and persistent viraemia should raise the possibility of ganciclovir resistance. This is especially likely to occur after prolonged exposure to ganciclovir with an incidence of up to 7% of patients [13]. More recently, Limaye has shown that the emergence of ganciclovir resistance is lower (< 4%) with valganciclovir use than previously reported with ganciclovir [14].

### **Second-line agents**

Only one study was found that had evaluated foscarnet in kidney transplant recipients. Ringden et al (1986) described the pharmacokinetics, safety and their preliminary clinical experiences using foscarnet in the treatment of cytomegalovirus infections in bone marrow and renal transplant recipients [15]. Fifty-seven episodes of severe CMV infection were treated with IV foscarnet in 13 bone marrow and 33 renal graft recipients. Multiple adverse effects were recorded including decreased haemoglobin, decreased renal function and increased serum calcium. Abnormal liver function tests, hallucinations and tremor were

seen in one uraemic patient with foscarnet levels > 400 mg/L. Improvements, such as eradication of CMV (8/14 assessable patients), resolution of fever (11/22), and improved laboratory values (13/23) were noted in 17/24 (70%) patients.

## **SUMMARY OF THE EVIDENCE**

Cytomegalovirus disease remains a significant problem following kidney transplantation. Identification of patients at higher risk of developing disease has led to several prophylactic and pre-emptive treatment stratagems. These are discussed in detail in the KHA-CARI guidelines on CMV prophylaxis and pre-emptive therapy.

Ganciclovir is the treatment of choice for CMV disease and should be administered intravenously with the dose modified according to creatinine clearance. It is unlikely that a randomised controlled trial will ever be undertaken to confirm the efficacy of IV ganciclovir compared with placebo. Treatment should be continued for at least 2 weeks or until CMV-DNA is not detectable. While immunosuppressive therapy is frequently reduced in patients with CMV disease, this measure has not been subjected to a clinical trial. Several clinical studies using mTOR inhibitors after renal transplantation have observed a reduced incidence of CMV disease and this warrants further study.

Oral ganciclovir has been used successfully to treat mild to moderate CMV disease but is no longer available for clinical use. The recent introduction of valganciclovir, with 10 times the bioavailability of oral ganciclovir and kinetics comparable to IV ganciclovir, may provide an alternative to IV therapy. Valganciclovir therapy in patients with milder forms of CMV disease has the potential to reduce hospital stay and the complications associated with prolonged IV access.

Ganciclovir resistance remains an important issue and has been reported in up to 7% of solid organ transplants and may be treated with second-line agents such as foscarnet and cidofovir. Both of these agents are associated with significant nephrotoxicity and side effects. There is no evidence to support the use of acyclovir, valaciclovir and CMV-Ig in renal transplant recipients. Failure to respond to therapy may be due to inadequate treatment, ganciclovir resistance or super-infection.

In the future, it is hoped that immunotherapies using vaccines to prevent CMV disease and adoptive transfer of CMV-specific T cells may provide additional treatment options for the critically ill patient who is unable to mount an immune response to CMV.

## **What do the other guidelines say?**

### **Kidney Disease Improving Global Outcomes, 2009 [16]:**

13.2.3.1: We recommend that all patients with serious (including most patients with tissue invasive) CMV disease be treated with intravenous ganciclovir. (1D)

13.2.3.2: We recommend that CMV disease in adult KTRs that is not serious (e.g. episodes that are associated with mild clinical symptoms) be treated with either intravenous ganciclovir or oral valganciclovir. (1D)

13.2.3.3: We recommend that all CMV disease in pediatric KTRs be treated with intravenous ganciclovir. (1D)

13.2.3.4: We suggest continuing therapy until CMV is no longer detectable by plasma NAT or pp65 antigenemia. (2D)

13.2.4: We suggest reducing immunosuppressive medication in life-threatening CMV disease, and CMV disease that persists in the face of treatment, until CMV disease has resolved. (2D)

13.2.4.1: We suggest monitoring graft function closely during CMV disease. (2D)

CMV, cytomegalovirus; KTRs, kidney transplant recipients; NAT, nucleic acid testing.

**International Herpes Management Forum, 2000 [17]:**

In any transplant recipient, CMV disease should be treated for 2-4 weeks with intravenous ganciclovir. Acyclovir is ineffective in treating established CMV disease in transplant recipients.

**IHMF Workshop, 2007:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**Canadian Society of Transplantation, 2005 [18]:**

Intravenous ganciclovir is the gold standard for CMV disease treatment;  
Adjust dose carefully and promptly for renal failure;  
Avoid dose adjustments for leukopaenia if possible.

Oral ganciclovir or acyclovir should not be used for treatment.

Valganciclovir theoretically could replace IV ganciclovir but studies to validate this approach are required (induction therapy with IV).

Adjunctive CMV Ig is recommended by some experts in severe CMV disease (pneumonitis, severe GI disease), or when the patient is hypogammaglobulinemic.

Immunosuppression should be reduced if possible.

Laboratory monitoring of CMV viral load during therapy is essential to document resistance and monitor response.

Initial monitoring should occur at 1 week after treatment onset.

Treatment should continue for at least 1 week after CMV viral load is documented to be undetectable.

If secondary prophylaxis is used, viral load monitoring is essential to detect development of resistance.

**British Renal Association:** No recommendation.

**British Transplantation Society, 2011 [19]:**

Patients with CMV disease should receive intravenous ganciclovir or oral valganciclovir until resolution of symptoms and for a minimum of 14 days (1B).

Foscarnet and cidofovir are second line therapeutic options unless ganciclovir resistance has been demonstrated (Not graded, B).

Consideration should be given to a reduction in immunosuppression (Not graded, D).

After treatment doses have been administered, an additional 1-3 months of appropriate prophylaxis should be considered to minimise the risk of recurrent infection (Not graded, D).

The duration and efficacy of treatment should be determined using PCR monitoring of viral load (1B).

**European Best Practice Guidelines, Renal Transplantation (Part 1), 2000 [20]:**

H. All recipients with documented CMV disease (symptomatic CMV infection) must receive a curative treatment. Currently, the only validated treatment is IV ganciclovir at a daily dose of 5 mg/kg twice daily, adjusted to GFR, for at least 14 days (Evidence level A). Alternatively, they may receive IV ganciclovir for at least 5 days followed by oral ganciclovir at a daily dose of 1000 mg three times daily for a longer period (2-12 weeks) (Evidence level B).

**European Society of Urology, 2009:** No recommendation.

**The American Society of Transplantation, 2009 [21]:**

- (1) In any solid transplant recipient, CMV disease should be treated with either intravenous ganciclovir (5 mg/kg two times a day) (I) or oral valganciclovir (900 mg two times a day) (I) until the following criteria are met:
  - a. Clinical resolution of symptoms and;
  - b. Virologic clearance below a threshold negative value (test specific; see text); monitor patients with viral load or pp65 antigenemia once a week and ;
  - c. Minimum 2 weeks of treatment.
- (2) Intravenous ganciclovir is preferable to oral valganciclovir in patients with severe or life-threatening disease, or in patients who may have a problem with gastrointestinal absorption of oral drug (e.g. significant diarrhea).
- (3) Acyclovir and oral ganciclovir are not effective in treating CMV disease in transplant recipients (II-2). Oral ganciclovir treatment in the presence of CMV replication may lead to emergence of ganciclovir resistant CMV strains (II-2).
- (4) It is unclear whether addition of IVIG or CMVIG to existing treatment regimens has a benefit for solid organ transplant recipients (II-2) but may be considered for patients with CMV pneumonitis and possibly other severe forms of disease.
- (5) After completion of treatment, a 1-3 month course of secondary prophylaxis may be considered depending on the clinical situation (III). Alternatively, close clinical and/or virologic follow-up after discontinuation of treatment is an option (III).

## **SUGGESTIONS FOR FUTURE RESEARCH**

1. Perform a study to assess the efficacy of IV ganciclovir/introduction of new agents.
2. All new anti-CMV therapy should be tested in RCTs with one arm receiving IV ganciclovir.
3. Run studies of molecular markers of disease activity to determine the optimal duration of therapy.
4. Investigate post-treatment prevention to reduce recurrence. Give oral therapy to high-risk patients?
5. Establish the relationship between ganciclovir exposure and prophylaxis and the emergence of ganciclovir resistance.

## **CONFLICT OF INTEREST**

David Goodman has a Level II b conflict of interest according to the conflict of interest statement set down by KHA-CARI.

---

## References

1. Asberg A, Humar A, Rollag H et al. Oral valganciclovir is non inferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2007; **7**: 2106-13.
2. Asberg A, Humar A, Jardine A et al. VICTOR Study Group. Long-term outcomes of CMV disease treatment with valganciclovir versus IV ganciclovir in solid organ transplant recipients. *Am J Transplant* 2009; **9**: 1205-13.
3. Sagedal S, Nordal KP, Hartmann A et al. A prospective study of the natural course of cytomegalovirus infection and disease in renal allograft recipients. *Transplantation* 2000; **70**: 1166-74.
4. Rondeau E, Farquet C, Fries D et al. Treatment of cytomegalovirus infections with ganciclovir in kidney transplant recipients. Clinical and pharmacokinetic study. *Presse Medicale* 1991; **20** (40): 2030-32.
5. Jordan SC, Vo A, Bunnapradist S et al. Treatment of active cytomegalovirus disease with oral ganciclovir in renal allograft recipients: monitoring efficacy with quantitative cytomegalovirus polymerase chain reaction. *Am J Transplant* 2002; **2**: 671-73.
6. Pescovitz MD, Rabkin J, Merion R et al. Valganciclovir provides ganciclovir plasma exposure similar to IV ganciclovir in transplant recipients [abstract]. *Transplantation* 1999; **67** (Suppl 7): S126.
7. Humar A, Siegal D, Moussa G et al. A prospective assessment of valganciclovir for the treatment of cytomegalovirus infection and disease in transplant recipients. *J Infect Dis* 2005; **192**: 1154-57.
8. Len O, Gavalda J, Aguado JM et al. RESITRA. Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; **46**: 20-27.
9. Sawyer MD, Mayoral JL, Gillingham KJ et al. Treatment of recurrent cytomegalovirus disease in patients receiving solid organ transplants. *Arch Surg* 1993; **128**: 165-69.
10. Sia IG, Wilson JA, Groettum CM et al. Cytomegalovirus (CMV) DNA load predicts relapsing CMV infection after solid organ transplantation. *J Infect Dis* 2000; **181**: 717-20.
11. Eida AK, Arthursa SJ, Dezielb PP et al. Clinical predictors of relapse after treatment of primary gastrointestinal cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2010; **10**: 157–61.
12. Arend SM, Westendorp RG, Kroon FP et al. Rejection treatment and cytomegalovirus infection as risk factors for *Pneumocystis carinii* pneumonia in renal transplant recipients. *Clin Infect Dis* 1996; **22**: 920-25.
13. Limaye AP, Corey L, Koelle DM et al. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; **356**: 645-49.
14. Limaye AP. Antiviral resistance in cytomegalovirus: an emerging problem in organ transplant recipients. *Sem Respir infect* 2002; **17**: 265-73.
15. 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.
16. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant* 2009; **9** (Suppl 3): S1-S155.
17. International Herpes Management Forum. Management guidelines: the challenge of CMV infection and disease in transplantation. Cambridge: Cambridge Medical Publications; 2000.

18. Preiksaitis JK, Brennan DC, Fishman J, Allen U. Canadian Society of Transplantation Consensus Workshop on Cytomegalo virus Management in Solid Organ Transplantation Final Report. *Am J Transplant* 2005; **5**: 218-27.
19. Newstead CG, Emery VC, Andrews PA et al. British Transplantation Society Guidelines for the Prevention and Management of Cytomegalovirus Disease after Solid Organ Transplantation. 3<sup>rd</sup> ed. London: British Transplantation Society; 2011.
20. Berthoux F, Abramowicz D, Bradley B et al. European Best Practice Guidelines for Renal Transplantation (Part 1). EBPG Expert Group on Renal Transplantation. *Nephrol Dial Transplant* 2000; **15** (Suppl 7): S52-S85.
21. Humar A, Snyderman D, and the AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplant recipients. *Am J Transplant* 2009; **9** (Suppl 4): S78-S86.

**Table 1 Characteristics of included studies**

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Asberg et al 2009	321	Randomised controlled clinical trial	42 centres, international	Solid organ transplant recipients with CMV disease	2 x day IV ganciclovir	Oral valganciclovir for 21 days	12	
Asberg et al 2007	321	Randomised controlled clinical trial	42 centres, international	Solid organ transplant recipients with CMV disease	IV ganciclovir	Oral valganciclovir	-	(see Asberg 2009)
Humar et al 2005	64	Case control study	Single centre, Canada	Organ transplant recipients with CMV disease	IV ganciclovir	Oral valganciclovir	1	
Len et al 2007	3467	Prospective comparative cohort study	Multicentre, Spain	Solid organ transplant recipients	Ganciclovir	Valganciclovir	24	

**Table 2 Quality of randomised trials**

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to- treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Asberg et al 2009	Not specified	No	No	No	Yes	5.8

**Table 3 Results for dichotomous outcomes**

Study ID (author, year)	Outcomes	Intervention group (no. of patients with events/no. of patients exposed)	Control group (no. of patients with events/no. of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Asberg et al 2009	Death	9/157	11/164	0.85 (0.36, 2.01)	-0.01 (-0.06, 0.04)
Asberg et al 2009	Opportunistic infection	13/157	11/164	1.23 (0.57, 2.67)	0.02 (-0.04, 0.07)
Asberg et al 2009	CMV disease at 12 months (prevalence)	5/110	3/106	1.61 (0.39, 6.55)	-0.01 (-0.05, 0.03)