

Prophylaxis for Cytomegalovirus infection in patients following renal transplantation

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GUIDELINES

- a. Prophylactic treatment for Cytomegalovirus (CMV) is recommended in solid organ transplantation as it is associated with a significant decrease in CMV disease and infection compared with placebo or no treatment (approximately a 50% and 40% decrease in relative risk, respectively) (Level I evidence).
- b. The use of the antiviral agents oral valganciclovir, oral valaciclovir, and intravenous ganciclovir, is recommended (Level II evidence). The addition of anti-CMV immunoglobulin to these agents is not recommended as there is no additional benefit (Level I evidence).
- c. On the pre-transplant CMV antibody assay, prophylaxis for CMV disease is indicated for the following donor/recipient subgroups:
 - D+ and R+
 - D+ and R-
 - D-/R+
 - but not when Donor and Recipient are both negative.
- d. In high risk, D+/R- recipients, it is recommended that the duration of prophylaxis be extended from 3 to 6 months as it significantly reduces CMV disease and viraemia.

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **Cost-effectiveness:** In D+/R- recipients, 6-month compared with 3-month prophylaxis was cost-effective in reducing CMV infection and disease.
- There is no indication for the use of Immunoglobulin in prophylaxis of CMV disease in solid organ transplant recipients.
- **Dosing:** In the reported studies, total daily doses of antiviral agents used were as follows and were reduced for impaired renal function:
 - oral valaciclovir 3200 mg
 - oral valganciclovir 900 mg, and
 - intravenous ganciclovir 5-10 mg/kg for an average of 14 days.*Note:* Oral ganciclovir is no longer available in Australia.
- Prophylaxis is also indicated when using T cell-depleting antibody separate to routine prophylaxis as described above.

IMPLEMENTATION AND AUDIT

No recommendation.

BACKGROUND

Cytomegalovirus is the most frequent viral infection following renal transplantation with evidence of infection found in at least two-thirds of patients.

Cytomegalovirus belongs to the group of herpesviruses and is a common infection in the community, with about 80% of adults showing seropositivity to the virus. [1] The major determinants of infection are evidence of virus in the donor, the presence of latency (seropositivity) in the recipient, and the type of immunosuppressive regimen administered. It is usual to make a distinction between infection and disease where disease is characterised by evidence of organ damage and infection is by detection of virus, with or without disease.

Cytomegalovirus disease is associated with increased morbidity and mortality, whereas infection alone may be associated with an increased risk of transplant rejection and bacterial and fungal infection. [2-4] These consequences have led to interventions for prophylaxis, early diagnosis and treatment.

The objectives of this guideline are to provide evidence to support/identify:

- the use of CMV prophylaxis in preventing primary infection or re-activation of latent infection
- the best agents to reduce infection and disease
- the duration of therapy
- the cost-effectiveness of therapy, and
- the effect of prophylaxis on acute rejection.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for cytomegalovirus were combined with MeSH terms and text words for organ transplantation and combined with MeSH terms and text words for antiviral agents and prophylaxis. The search was carried out in Medline (1966 – January Week 1, 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search: 7 January 2009.

WHAT IS THE EVIDENCE?

Antiviral agents: Meta-analyses

A Cochrane review of CMV prophylaxis with antiviral agents for solid organ transplantation was reported by Couchoud [5] and updated by Hodson et al in 2008. [6] The latter meta-analysis included 34 studies with 3850 patients and looked at prophylaxis using acyclovir, ganciclovir and valganciclovir compared with placebo or no treatment. These trials consisted of all solid organ transplants and were limited to antiviral medications. They excluded trials using other interventions such as immunoglobulins, interferons and vaccination. The Cochrane review searched the usual databases up to February 2007.

Prophylaxis significantly reduced CMV disease, CMV infection, all-cause mortality, and other infections such as those caused by HSV, bacteria and protozoa. There was no reduction in acute rejection or graft loss. Seven studies looked at direct comparison of antiviral agents. Ganciclovir was more effective than acyclovir and there were no differences between IV ganciclovir and oral valganciclovir.

Subgroup analysis of pre-transplant antibody status (donor: D + or – and recipient: R + or –) in the

first Cochrane review showed significant reduction in disease in D + and R + or – groups. [5] In D – R + groups, a reduction in disease was observed but this did not reach statistical significance. There was no significant reduction in infection in any subgroup. However, numbers were small, with less than 100 in each group. Although subgroup analysis between ganciclovir and acyclovir did not show any difference in disease, there was a significant difference in infection with ganciclovir (RR 0.52; CI: 0.42-0.64 for ganciclovir and RR 0.80; CI: 0.60-1.05 for acyclovir).

A smaller meta-analysis conducted by Kalil et al, found 17 trials with 1980 recipients of solid organ transplants. [7] Compared with placebo or no therapy, acyclovir and ganciclovir prophylaxis reduced CMV disease (OR 0.20; CI: 0.13-0.31). This study also found that both prophylactic and pre-emptive strategies significantly reduced allograft rejection.

Antiviral agents: Other randomised controlled trials

Oral acyclovir versus oral ganciclovir trials [8,9] show ganciclovir to be a superior agent for the prevention of disease. Valaciclovir versus placebo [10, 11] shows similar results to the Cochrane review. Another randomised controlled trial (RCT) comparing oral ganciclovir and valaciclovir with controls or no therapy showed no significant differences, with both treatment arms being superior to controls for CMV disease, infection and treatment failure (death, graft loss, disease or withdrawal). [12]

In 2004, Paya et al reported a double-blind, double-dummy, clinical study comparing oral ganciclovir and oral valganciclovir in 301 high-risk (D+/R-) recipients of solid organ transplants. [13] The results showed that the agents were equivalent in terms of CMV disease, viraemia, acute rejection, graft loss and acute rejection after CMV disease. Those treated with valganciclovir had a slight increase in neutropaenia (8.2% vs. 3.2%). The time to onset of CMV disease was delayed in the valganciclovir group at 6 months but they were equal at 12 months. The pharmacokinetic study showed that valganciclovir patients achieved a higher area under the curve (AUC) by 1.7%.

Antiviral agents: Other studies

A retrospective study in a single centre by Akalin et al (2003) of 129 kidney and kidney/pancreas recipients also showed equivalence between oral valganciclovir and ganciclovir. [14] An RCT with ganciclovir vs. placebo showed reduction in CMV during T cell depleting therapy following transplantation. [15]

Immunoglobulin therapy

The Cochrane Review of immunoglobulin, vaccines or interferon for preventing CMV disease in solid organ transplant recipients first published in 2007 by Hodson et al, included 37 studies with 2185 recipients. [16] There was no significant difference in CMV disease, CMV infection or all-cause mortality with immunoglobulin (Ig), vaccine or interferon compared with placebo/no therapy, although Ig significantly reduced death from CMV disease. Likewise, there were no differences between Ig combined with antivirals compared with antivirals alone.

Another smaller meta-analysis of solid organ transplant recipients by Bonaros et al [17] included 11 trials with 698 recipients in which Ig was used in one arm and in three was used with acyclovir. They showed improved total survival (RR 0.67; CI: 0.47-0.95), reduced CMV disease (RR 0.70; CI: 0.57-0.85) and reduced CMV-associated deaths (RR 0.45; CI: 0.24-0.84) but in the renal transplant subgroup there was no survival benefit (RR 0.35; CI: 0.12-1.04). However, an RCT of immune globulin versus no treatment reported by Snyderman et al in D +/R – renal transplant recipients shows reduction in CMV disease from 60% to 21% (P < 0.01) but there was no reduction in CMV infection as measured by virus isolation or seroconversion. [18]

Organ rejection

The meta-analysis by Kalil et al, showed that use of the antiviral agents acyclovir or ganciclovir, as prophylaxis or pre-emptive therapy, reduced acute rejection compared with placebo or no treatment (OR 0.74; CI: 0.59-0.94 for prophylaxis and OR 0.47; CI: 0.24-0.91 for pre-emptive treatment). [7]

A prospective, randomised trial of 3-month therapy with oral ganciclovir, valganciclovir or deferred therapy in 83 subjects, showed a reduction in acute rejection in both antiviral groups compared with the deferred group (incidence rates of 6%, 3% and 67%, respectively; $P < 0.001$). There was no difference between the antiviral therapy groups. [19]

The Cochrane meta-analysis found no difference in rejection rates. [5,6]

Duration of therapy

There are no RCTs that compare duration of therapy in all recipients. One RCT comparing acyclovir and ganciclovir in liver transplant recipients, with 3 months prophylaxis, shows that protection against CMV disease lasts up to 1 year [20]. These authors mention that their regimen was not associated with ganciclovir resistance.

A retrospective study of a consecutive cohort of 3 months' and 6 months' prophylaxis in 222 seronegative recipients of seropositive kidney and/or pancreas transplant patients (who were followed up for 12 months following cessation of therapy) showed a significant reduction of CMV disease in the 6-month group (HR 0.35; CI: 0.17-0.72). [21]

A new study, the IMPACT Study, [22] reported that in high risk D+/R- recipients randomised to 3 or 6 months' valganciclovir prophylaxis, there was significantly less disease and viraemia with 6 months compared with 3 months of therapy. This trial has been criticised [23] for its design and analysis, with those authors concluding that it does not have the strength of evidence to change practice.

Cost-effectiveness

Luan et al also looked at the cost-effectiveness of prophylaxis versus pre-emptive therapy. In D+/R- recipients, 6-months' compared with 3-months' prophylaxis was cost-effective in reducing CMV infection and disease. [24]

Cytomegalovirus drug resistance

In a separate report of the study by Paya et al [12], Boivin et al [25] prospectively screened for ganciclovir resistance by UL97 and UL54 gene sequencing on CMV DNA positive sera (these sequences would detect most reported resistance mutations). Cytomegalovirus resistance did not emerge with valganciclovir and of 3 patients in the ganciclovir group with gene sequence positivity, there were no clinical consequences and all three cleared the virus.

SUMMARY OF THE EVIDENCE

Please refer to the enclosed evidence tables.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: [26] December 2009 (13.2.1). CMV prophylaxis:

We recommend that Kidney Transplant Recipients (except when donor and recipient both have negative CMV serologies) receive chemoprophylaxis for CMV infection with oral ganciclovir or valganciclovir for at least 3 months after transplantation (level 1B) and for 6 weeks after treatment with a T-cell-depleting antibody (level 1C).

The use of valacyclovir and acyclovir should be restricted to situations where ganciclovir/valganciclovir cannot be used.

British Renal Association: No recommendation.

British Transplant Society: [27] March 2011.

For renal transplant recipients, the recommended management strategy is one of:

- a) Oral valganciclovir for at least 100 days (1 A), or
- b) Oral valganciclovir for 200 days (2 B),
- c) Oral valacyclovir for 90 days (2 A),
- d) Intravenous ganciclovir for 28 days (2 A),
- e) Serial measurements of viral load and treatment with oral valganciclovir or intravenous ganciclovir when levels predictive of disease are reached (2 A).

No prophylaxis against primary infection is recommended for D+/R+ unless anti-T cell therapy is used.

Canadian Society of Nephrology: No recommendation.

Canadian Society of Transplantation: [28] November 2004. Universal prophylaxis. One of the following:

- a) Oral ganciclovir (3g/day) [A1]
- b) Valganciclovir (900mg/day) [A1]
- c) IV ganciclovir (5mg/kg/day)
- d) Oral valacyclovir (8g/day) is an alternative.

European Best Practice Guidelines: December 2000. CMV prophylaxis is recommended for the seronegative recipients of a seropositive donor kidney and for seropositive recipients receiving antibody treatment as induction or therapy for acute rejection. Prophylaxis must be selected from the following five validated modalities:

- a) Weekly intravenous infusions of hyperimmune globulins for 6 weeks (at high dose) or for 16 weeks (at low dose).
- b) Oral acyclovir for 12 weeks at a daily dose of 3200 mg adjusted for renal function.
- c) Oral valacyclovir for 90 days at a daily dose of 8000 mg adjusted for renal function.
- d) Ganciclovir administered intravenously for at least 14 days at a dose of 10 mg/kg/day adjusted for renal function.
- e) Oral ganciclovir for 2-12 weeks at a daily dose of 3000 mg adjusted for renal function. [29]

European Association of Urology: Guidelines on Renal Transplantation. March 2009. Accessed at: http://www.uroweb.org/gls/pdf/23_Renal_Transplant%202009.pdf (July 2011)

No recommendation.

American Society of Transplantation (incorporating KDIGO Guidelines for the Care of Kidney Transplant Recipients): Update published December 2009. Am J Transplant 2009; Vol 9, Supplement 3. CMV Prophylaxis – Recommend chemoprophylaxis with oral ganciclovir, valganciclovir, or valacyclovir for at least 3 months after transplantation (Level 1 evidence). Except prophylaxis is generally not needed when donor and recipient both have negative serology, provided CMV negative blood or leukocyte-depleted blood products are used.[30, 31]

SUGGESTIONS FOR FUTURE RESEARCH

1. Conduct studies to determine the optimal duration of therapy of antiviral agents.
2. Conduct studies to determine the optimum dose of antiviral medications.
3. Conduct a trial of delayed versus immediate use of prophylaxis to induce CMV specific immunity.

CONFLICT OF INTEREST

Bruce Pussell has a Level II d conflict of interest according to the conflict of interest statement set down by KHA-CARI.

REFERENCES

1. Rubin RH. Infectious disease complications of renal transplantation. *Kidney Int* 1993; **44**(1): 221-36.
2. Dickenmann MJ, Cathomas G, Steiger J, et al. Cytomegalovirus infection and graft rejection in renal transplantation. *Transplantation* 2001; **71**(6): 764-67.
3. Tong CY, Bakran A, Peiris JS, et al. The association of viral infection and chronic allograft nephropathy with graft dysfunction after renal transplantation. *Transplantation* 2002; **74**(4): 576-78.
4. McLaughlin K, Wu C, Fick G, et al. Cytomegalovirus seromismatching increases the risk of acute renal allograft rejection. *Transplantation* 2002; **74**(6): 813-16.
5. Couchoud-Heyer C. Cytomegalovirus prophylaxis with antiviral agents for solid organ transplantation. Cochrane Database of Systematic Reviews 1998, Issue 4. Art. No.: CD001320. DOI: 10.1002/14651858. CD001320.pub2.
6. Hodson EM, Craig JC, Strippoli GFM, et al. Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD003774. DOI: 10.1002/14651858. CD003774.pub3.
7. Kalil AC, Levitsky J, Lynden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med* 2005; **143**: 870-80.
8. Flechner SM, Avery RK, Fisher R, et al. A randomised, prospective, controlled trial of oral acyclovir versus oral ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998; **66**: 1682-88.
9. Rubin RH, Kemmerly SA, Conti D, et al. Prevention of primary cytomegalovirus disease in organ transplant recipients with oral ganciclovir or oral acyclovir prophylaxis. *Transplant Infect Dis* 2000; **2**: 112-17.
10. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med* 1999; **340**: 1462-70.
11. Reischig T, Jindra P, Hes O, et al. Valaciclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. *Am J Transplant* 2008; **8**: 69-77.
12. Reischig T, Opatrny K Jr, Bouda M, et al. A randomized prospective controlled trial of oral ganciclovir versus oral valacyclovir for prophylaxis of cytomegalovirus disease after renal transplantation. *Transpl Int* 2002; **15**: 615-22.
13. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; **4**: 611-20.
14. Akalin E, Sehgal V, Ames S, et al. Cytomegalovirus disease in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis. *Am J Transplant* 2003; **3**: 731-35.
15. 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**(1): 18-26.
16. Hodson EM, Jones CA, Strippoli GFM, et al. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005129. DOI: 10.1002/14651858. CD005129.pub2.
17. Bonaros N, Mayer B, Schachner T, et al. CMV-hyperimmune globulin for preventing cytomegalovirus infection and disease in solid organ transplant recipients: a meta-analysis. *Clin Transplant* 2008; **22**: 89-97.
18. Snyderman 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.

19. Reischig T, Jindra P, Mares J, et al. Valaciclovir for cytomegalovirus prophylaxis reduces the risk of acute renal allograft rejection. *Transplantation* 2005; **79**: 317-24.
20. Winston DJ and Busuttil RW. Randomized controlled trial of oral ganciclovir versus oral acyclovir after induction with intravenous ganciclovir for long-term prophylaxis of cytomegalovirus disease in cytomegalovirus-seropositive liver transplant recipients. *Transplantation* 2003; **75**(2): 229-33.
21. Luan FL, Stuckey LJ, Park JM, et al. Six-month prophylaxis is cost effective in transplant patients at high risk for cytomegalovirus infection. *J Am Soc Nephrol* 2009; **20**: 2449–58.
22. Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant* 2010; **10**: 1228–37.
23. Kalil AC, Sun J, Florescu DF. IMPACT trial results should not change current standard of care of 100 days for cytomegalovirus prophylaxis. *Am J Transplant* 2010; **10**: 1-4.
24. Luan FL, Stuckey LJ, Park JM, et al. Six-month prophylaxis is cost effective in transplant patients at high risk for cytomegalovirus infection. *J Am Soc Nephrol* 2009; **20**: 2449-58.
25. Boivin G, Goyette N, Gilbert C, et al. Absence of cytomegalovirus-resistance mutations after valganciclovir prophylaxis in a prospective multicenter study of solid organ transplant recipients. *J Infect Dis* 2004; **189**: 1615-18.
26. Bia M, Adey DB, Bloom RD, et al. KDOQI recommendations in viral diseases. KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Kidney Dis* 2010; **56**(2): 189-218.
27. British Transplantation Society Guidelines for the Prevention and Management of CMV Disease after Solid Organ Transplantation. Third edition, March 2011. Available from: <http://www.bts.org.uk/transplantation/standards-and-guidelines/>
28. Preiksaitis JK, Brennan DC, Fishman J, et al. Canadian Society of Transplantation Consensus Workshop on Cytomegalovirus Management Final Report. *Am J Transplant* 2005; **5**: 218-27.
29. Berthoux F, Abramowicz D, Bradley B, et al. The transplant recipient from initial transplantation hospitalization to 1 year post transplant. European Best Practice Guidelines for Renal Transplantation (Part 1). *Nephrol Dial Transpl* 2000; **15** (Suppl 7): S71-S74.
30. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transplant* 2009; **9**(Suppl 3): S1–S157.
31. Humar A, Snyderman D, and AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplant recipients. In: *Transplant Infectious Disease Guidelines*, 2nd edition. *Am J Transplant* 2009; **9** (Suppl 4): S78-S86.

APPENDICES

Table 1. Characteristics of randomised controlled trials

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Flechner et al 1998	101	Randomised controlled clinical trial	Teaching hospital	Kidney transplant recipients	Oral ganciclovir 1000 mg tds x 84 days	Oral acyclovir 800 mg qds x 84 days	14.4	
Hibberd et al 1995	113	Randomised controlled clinical trial	Multicentre	Kidney transplant recipients positive for CMV	Ganciclovir	Placebo	6	
Lowance et al 1999	408	Randomised controlled clinical trial	University	Kidney transplant recipients	Oral valaciclovir 2 g qds x 90 days	Placebo	12	
Paya et al 2004	364	Randomised controlled clinical trial	University	Kidney, heart and liver transplant recipients	Oral valganciclovir 900 mg qd x 100 days	Oral ganciclovir 1000 mg tds x 100 days	12	
Reischig et al 2002	38	Randomised controlled clinical trial	Multicentre	Kidney transplant recipients	Oral valaciclovir 2 g qid x 12 weeks	Oral ganciclovir 1 g tds x 12 weeks	6	
Rubin et al 2000	155	Randomised controlled clinical trial	Multicentre	Kidney, heart and liver transplant recipients	Oral ganciclovir 1000 mg tds x 12 weeks	Oral acyclovir 400 mg tds x 12 weeks	12	
Snydman et al 1987	99	Randomised controlled clinical trial	University	Kidney transplant recipients	Intravenous CMV immunoglobulin prophylaxis 150 mg/kg of body weight within 72 hours of transplant, then 100 mg/kg ² at 2 and 4 weeks after transplant, then 50 mg/kg at 6, 8, 12 and 16 weeks after transplant	Placebo	12	
Winston & Busuttil 2003	64	Randomised controlled clinical trial	University	Liver transplant recipients	Oral ganciclovir 1000 mg tds x 86 days	Intravenous ganciclovir 6 mg/kg/day of body weight x 86 days	12	

Table 2. Quality of randomised controlled trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Flechner et al 1998	Adequate	No	No	NA*	Yes	0
Hibberd et al 1995	Adequate	No	No	No	Yes	1.8
Lowance et al 1999	Unclear	Yes	Yes	NA*	Yes	0
Paya et al 2004	Adequate	Yes	Yes	Yes	No	0
Reischig et al 2002	Adequate	No	No	NA	No	0
Rubin et al 2000	Adequate	No	No	NA	No	0
Snydman et al 1987	Unclear	Yes	Yes	NA	No	NA
Winston & Busuttil 2003	Unclear	No	No	NA	Yes	0

* NA = not available

Table 3. Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Flechner et al 1998	CMV disease	1/40	9/39	0.11 (0.01 to 0.82)	-0.21 (-0.35 to -0.06)
Hibberd et al 1995	Death	1/64	2/49	0.38 (0.04, 4.10)	-0.03 (-0.09, 0.04)
	CMV disease	9/64	16/49	0.43 (0.21, 0.89)	-0.19 (-0.34, -0.03)
Lowance et al 1999	CMV disease	18/306	60/310	0.30 (0.18 to 0.50)	-0.13 (-0.19 to -0.08)
Paya et al 2004	CMV disease	41/239	23/125	0.93 (0.59 to 1.48)	-0.01 (-0.10 to 0.07)
Reischig et al 2002	CMV disease	1/12	2/13	0.54 (0.06 to 5.24)	-0.07 (-0.32 to 0.18)
Rubin et al 2000	CMV disease	15/77	21/78	0.72 (0.40 to 1.30)	-0.07 (-0.21 to 0.06)
Snydman et al 1987	Virologically-confirmed CMV syndrome	5/24	21/35	0.35 (0.15 to 0.79)	-0.39 (-0.62 to -0.16)
Winston & Busuttil 2003	CMV disease	3/32	4/32	0.75 (0.18 to 3.09)	-0.03 (-0.18 to 0.12)