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Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients (Review)

Owers DS, Webster AC, Strippoli GFM, Kable K, Hodson EM

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[Intervention Review]

Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients

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ABSTRACT

Background

Cytomegalovirus (CMV) is a significant cause of morbidity and mortality in solid organ transplant recipients. Pre-emptive treatment of patients with CMV viraemia using antiviral agents has been suggested as an alternative to routine prophylaxis to prevent CMV disease. This is an update of a Cochrane review first published in 2005.

Objectives

This review was conducted to evaluate the efficacy of pre-emptive treatment with antiviral medications in preventing symptomatic CMV disease.

Search methods

For this update, we searched the Cochrane Renal Group's Specialised Register (to 16 January 2013) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised controlled trials (RCTs) of pre-emptive treatment compared with placebo, no specific treatment or with antiviral prophylaxis in solid organ transplant recipients.

Data collection and analysis

Four authors assessed the quality and extracted all data. Analyses used a random-effects model and results were expressed as risk ratio (RR) and 95% confidence intervals (CI).

Main results

We identified 15 eligible studies (1098 participants). Of these, six investigated pre-emptive treatment versus placebo or treatment of CMV when disease occurred (standard care), eight looked at pre-emptive treatment versus antiviral prophylaxis, and one reported on oral versus intravenous pre-emptive treatment.

Assessment of risk of bias identified that the processes reported for sequence generation and allocation concealment were at low risk of bias in only five and three studies, respectively. All studies were considered to be at low risk of attrition bias, and seven studies were considered to be at low risk of bias for selective reporting. Only one study reported adequate blinding of participants and personnel; no study reported blinding of outcome assessment.

Compared with placebo or standard care, pre-emptive treatment significantly reduced the risk of CMV disease (6 studies, 288 participants: RR 0.29, 95% CI 0.11 to 0.80) but not acute rejection (3 studies, 185 participants: RR 1.21, 95% CI 0.69 to 2.12) or all-cause mortality (3 studies, 176 participants: RR 1.23, 95% CI 0.35 to 4.30). Comparative studies of pre-emptive therapy versus prophylaxis showed no significant differences in preventing CMV disease between pre-emptive and prophylactic therapy (7 studies, 753 participants: RR 1.00, 95% CI 0.36 to 2.74) but there was significant heterogeneity ($I^2 = 63\%$). Leucopenia was significantly less common with pre-emptive therapy compared with prophylaxis (6 studies, 729 participants: RR 0.42, 95% CI 0.20 to 0.90). Other adverse effects did not differ significantly or were not reported. There were no significant differences in the risks of all-cause mortality, graft loss, acute rejection and infections other than CMV.

Authors' conclusions

Few RCTs have evaluated the effects of pre-emptive therapy to prevent CMV disease. Pre-emptive therapy is effective compared with placebo or standard care. Despite the inclusion of five additional studies in this update, the efficacy of pre-emptive therapy compared with prophylaxis to prevent CMV disease remains unclear due to significant heterogeneity between studies. Additional head-to-head studies are required to determine the relative benefits and harms of pre-emptive therapy and prophylaxis to prevent CMV disease in solid organ transplant recipients.

PLAIN LANGUAGE SUMMARY

Pre-emptive treatment with antiviral agents can help to reduce the risk of cytomegalovirus disease

Cytomegalovirus (CMV) is the most common cause of viral disease in people who have received kidney, heart, liver, lung or pancreas transplants (solid organ transplants). CMV is a major cause of illness and death during the first six months after transplantation. Characteristics of CMV include fever, very low white blood cell counts (leucopenia) and very low numbers of platelets (thrombocytopenia) with or without specific organ involvement.

Two main strategies to prevent CMV disease have been adopted: giving daily low doses of an antiviral agent (prophylaxis) to all organ transplant recipients, or prescribing an antiviral agent when an organ transplant recipient develops laboratory-confirmed evidence of infection during routine screening (pre-emptive treatment).

This review looked at the benefits and harms of pre-emptive treatment with antiviral agents in preventing CMV disease in solid organ transplant recipients. We identified six studies (288 participants) that compared pre-emptive treatment with placebo or usual care. Pre-emptive treatment significantly reduced the risk of CMV disease. There were also eight studies (784 participants) that compared pre-emptive treatment with antiviral prophylaxis. There were no significant differences in the risks of CMV disease or death between pre-emptive therapy and prophylaxis. However, variation in results among studies meant that there is some uncertainty about these results.

Low white blood cell counts were much less common with pre-emptive treatment.

More studies comparing pre-emptive treatment with antiviral prophylaxis are still required to provide greater certainty about the relative effectiveness of pre-emptive therapy compared with prophylaxis.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Pre-emptive medication for cytomegalovirus (CMV) viraemia compared to placebo/no treatment to prevent CMV disease in solid organ transplant recipients

Pre-emptive medication for CMV viraemia versus placebo/no treatment to prevent CMV disease in solid organ transplant recipients

Patient or population: solid organ transplant recipients with CMV viraemia
Settings: tertiary hospitals
Intervention: pre-emptive medication for CMV viraemia to prevent CMV disease
Comparison: placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Risk ratio (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Pre-emptive medication for CMV viraemia				
All symptomatic CMV disease	Study population		0.29 (0.11 to 0.8)	288 (6)	⊕⊕⊕⊕ low ^{1,2}	
	295 per 1000	85 per 1000 (32 to 236)				
	Moderate					
	359 per 1000	104 per 1000 (39 to 287)				
CMV organ involvement	Study population		0.41 (0.06 to 2.63)	217 (5)	⊕⊕⊕⊕ low ^{1,2}	
	107 per 1000	44 per 1000 (6 to 282)				
	Moderate					
	48 per 1000	20 per 1000 (3 to 126)				
Acute rejection	Study population		1.21 (0.69 to 2.12)	185 (3)	⊕⊕⊕⊕ low ^{1,2}	
	172 per 1000	208 per 1000 (119 to 365)				

	Moderate			
	191 per 1000	231 per 1000 (132 to 405)		
All-cause mortality	Study population	1.23 (0.35 to 4.3)	176 (3)	⊕⊕⊕⊕ low ^{1,2}
	45 per 1000	55 per 1000 (16 to 193)		
	Moderate			
	26 per 1000	32 per 1000 (9 to 112)		
Graft loss	Study population	0.28 (0.01 to 5.35)	36 (1)	⊕⊕⊕⊕ very low ^{1,2}
	95 per 1000	27 per 1000 (1 to 510)		
	Moderate			
	95 per 1000	27 per 1000 (1 to 508)		
Leucopenia	Study population	1.54 (0.16 to 15.36)	114 (2)	⊕⊕⊕⊕ low ^{1,2}
	17 per 1000	26 per 1000 (3 to 260)		
	Moderate			
	24 per 1000	37 per 1000 (4 to 369)		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative risk** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate

¹No studies used blinding of participants, investigators and outcome assessors and most reported unclear allocation concealment

²Small patient numbers

Summary of findings 2. Pre-emptive medication compared to prophylaxis for cytomegalovirus (CMV) viraemia to prevent CMV disease in solid organ transplant recipients

Pre-emptive medication versus prophylaxis for CMV viraemia to prevent CMV disease in solid organ transplant recipients

Patient or population: solid organ transplant recipients with CMV viraemia

Settings: tertiary hospitals

Intervention: pre-emptive medication for CMV viraemia to prevent CMV disease

Comparison: prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Risk ratio (95% CI)	No of partici- pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prophylaxis	Pre-emptive medication				
All symptomatic CMV disease	Study population		1.02 (0.43 to 2.44)	753 (7)	⊕⊕⊕⊕ low ^{1,2}	
	106 per 1000	108 per 1000 (45 to 258)				
	Moderate					
	88 per 1000	90 per 1000 (38 to 215)				
All-cause mor- tality	Study population		1.19 (0.56 to 2.51)	753 (7)	⊕⊕⊕⊕ low ^{1,3}	
	33 per 1000	39 per 1000 (18 to 82)				
	Moderate					
	29 per 1000	35 per 1000 (16 to 73)				
Graft loss	Study population		1.07 (0.41 to 2.82)	753 (7)	⊕⊕⊕⊕ low ^{1,3}	
	51 per 1000	55 per 1000 (21 to 145)				

	Moderate			
	55 per 1000	59 per 1000 (23 to 155)		
Acute rejection	Study population	1.23 (0.75 to 2.03)	693 (6)	⊕⊕⊕⊕ low ^{1,3}
	165 per 1000	203 per 1000 (124 to 334)		
	Moderate			
	166 per 1000	204 per 1000 (125 to 337)		
Leucopenia	Study population	0.42 (0.2 to 0.9)	729 (6)	⊕⊕⊕⊕ moderate ¹
	238 per 1000	100 per 1000 (48 to 214)		
	Moderate			
	207 per 1000	87 per 1000 (41 to 186)		
D+/R- serostatus: symptomatic CMV	Study population	0.99 (0.12 to 8.02)	39 (2)	⊕⊕⊕⊕ very low ^{1,3}
	150 per 1000	149 per 1000 (18 to 1000)		
	Moderate			
	94 per 1000	93 per 1000 (11 to 754)		
D+ or D-/R+ serostatus: symptomatic CMV	Study population	0.21 (0.02 to 1.76)	93 (2)	⊕⊕⊕⊕ very low ^{1,3}
	87 per 1000	18 per 1000 (2 to 153)		
	Moderate			
	85 per 1000	18 per 1000		

(2 to 150)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative risk** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate

¹No studies reported blinding of participants, investigators or outcome assessors and most did not report adequate allocation concealment

²Significant heterogeneity between studies

³Small numbers of events

BACKGROUND

Description of the condition

Cytomegalovirus (CMV) infection is an important cause of morbidity and mortality in solid organ transplant recipients, with up to 75% of patients developing or reactivating infection after transplantation (Fishman 2007). The risk of developing CMV is well established. CMV infection and disease are seen most commonly in CMV negative recipients of CMV seropositive organs and in recipients treated with anti-lymphocyte therapy (EBPG 2000). Recipients who have a positive serostatus for CMV, regardless of donor status, are at intermediate risk of developing or re-developing CMV; donor negative organs and negative serostatus recipients are at the lowest risk of infection (Fishman 2007).

CMV can lead to direct or indirect effects of infection. Direct effects include CMV syndrome (encompassing fever, myelosuppression, myalgia and arthralgia), tissue invasive CMV disease leading to hepatitis, gastroenteritis, pneumonitis and potentially any other organ or body tissue, and finally, mortality (Eid 2010). CMV infection may also be associated with indirect effects including acute and chronic organ rejection, graft loss, opportunistic infections other than CMV, and new onset diabetes mellitus (Eid 2010; Kotton 2010).

Description of the intervention

Pre-emptive therapy involves the detection of active CMV replication through routine surveillance using an appropriately sensitive and specific test (such as real-time polymerase chain reaction (PCR) or pp65 antigenaemia assay) with established thresholds for CMV infection. Once the CMV infection threshold has been reached, treatment with antiviral medications (valganciclovir or ganciclovir) is initiated with the aim of preventing progression to symptomatic CMV disease (Humar 2009).

How the intervention might work

The intervention aims to direct treatment to patients who are most at risk of developing CMV disease, rather than administering universal prophylaxis that would include some patients who would never develop CMV disease. By targeting higher risk patients it should be possible to direct therapy to those in need, to reduce the risk of adverse effects associated with long-term antiviral therapy, and possibly, to lower the cost of therapy. Pre-emptive therapy may also reduce the numbers of patients who develop late onset CMV disease after prophylaxis is ceased (Eid 2010).

Why it is important to do this review

Pre-emptive treatment of recipients with CMV viraemia detected on surveillance has been advocated as an alternative to antiviral prophylaxis because only recipients who develop CMV infection, and are thus at high risk of CMV disease, are treated. This approach exposes patients to a lower risk of adverse effects of medications and may reduce the risk of the emergence of resistant strains of CMV and of late onset CMV disease, which has been reported as increasing in frequency in solid organ transplant recipients (Arthurs 2007; Arthurs 2008; Eid 2010; Kotton 2010). Late onset CMV disease is seen in about 10% of patients given 12 weeks of oral ganciclovir prophylaxis but is rare following pre-emptive regimens.

It has been argued that pre-emptive treatment in CMV negative recipients of CMV positive organs allows controlled viral replica-

tion to occur before antiviral medications are administered (Limaye 2000). This could result in the development of specific immune responses which are important in the prevention of future episodes of CMV disease.

Pre-emptive therapy appears particularly attractive in recipients at low risk of CMV disease such as CMV positive recipients of kidney transplants who are not receiving antibody immunosuppression because their risk of CMV disease is only about 7% (Waiser 1998). However, pre-emptive therapy relies on the timely availability of sensitive and reliable methods for detecting CMV viraemia so that treatment based on identifying CMV infection can be initiated before CMV disease develops. Furthermore, the cost of screening may be higher than prophylaxis even though the cost of antiviral medication is lower (Eid 2010). Pre-emptive therapy potentially exposes patients to periods of CMV infection and possibly indirect effects of CMV infection. Moreover, treatment method relies on the patient's compliance with regular screening and easy access to a transplant centre if treatment is required.

Prophylaxis is currently the predominant intervention used to prevent CMV disease. Routine antiviral prophylaxis is associated with an increased risk of adverse effects of medications, the development of CMV resistance and late onset CMV disease when prophylaxis is discontinued and is costly (Arthurs 2008; Emery 2001; Hart 2001). Prophylaxis for all organ transplant recipients (except CMV negative recipients of CMV negative donors) means that a proportion of patients will receive potentially harmful medications when they were not destined to develop CMV disease.

In view of the actual and potential advantages and disadvantages of pre-emptive therapy and of prophylaxis to prevent CMV disease, a systematic review was warranted to ascertain the efficacy of pre-emptive therapy and the relative benefits and harms of these therapies for preventing CMV disease in solid organ transplant recipients.

This Cochrane systematic review should be considered in conjunction with the Cochrane review *Antiviral therapy for preventing CMV disease in solid organ transplants recipients* (Hodson 2013) which looked at the benefits and harms of prophylaxis with antiviral medications to prevent CMV disease. Hodson 2013 includes 37 studies (4342 participants). Prophylaxis with ganciclovir, valganciclovir or aciclovir (19 studies, 1981 participants) significantly reduced the risk of CMV disease, CMV infection and all-cause mortality compared with placebo or no specific therapy. In direct comparison studies, ganciclovir was significantly more effective than aciclovir (7 studies, 1113 participants). Valganciclovir was as effective as ganciclovir (1 study, 364 participants) and extended duration valganciclovir significantly reduced the risk of CMV disease compared with three months (2 studies, 454 participants).

OBJECTIVES

The aim of this review was to evaluate the benefits and harms of pre-emptive treatment of CMV viraemia to prevent CMV disease, all-cause mortality and the indirect effects of CMV infection (acute rejection, graft loss, opportunistic infections) in solid organ transplant recipients and to assess the comparative effects of pre-emptive treatment regimens and routine CMV prophylaxis with antiviral medications.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs (trials in which allocation was obtained by alternation, alternate medical records, date of birth or other predictable methods) only.

Types of participants

Studies enrolling any type of solid organ transplant recipient, adult or paediatric, were included.

Types of interventions

We included RCTs of pre-emptive treatment compared with placebo or standard care, pre-emptive treatment compared with antiviral prophylaxis, and different pre-emptive treatment regimens (different antiviral agents used for pre-emptive treatment, different doses, different routes of administration) in solid organ transplant recipients.

Types of outcome measures

The effects of these interventions were tested on the following outcomes:

- all-cause mortality
- death due to CMV disease
- CMV disease
- time to development of CMV disease
- graft loss
- acute rejection
- other infections
- adverse effects of medications.

For the purpose of analysis, pre-emptive treatment was defined as routine testing for CMV viraemia using any test and commencing antiviral treatment if viraemia was detected. Prophylaxis was defined as the regular administration of an appropriate antiviral medication for a period of time immediately post transplantation.

Other definitions for the meta-analysis were comparable with those reported previously by [Ljungman 2002](#). CMV infection was defined as isolation of CMV in any tissue or body fluid by an appropriately sensitive and specific test. CMV DNAemia was defined as detection of CMV DNA in whole blood, plasma, peripheral blood leukocytes or buffy coat specimens by an appropriately sensitive and specific technique such as real time polymerase chain reaction (RT-PCR). CMV disease was defined as CMV infection together with CMV syndrome (fever and bone marrow suppression) and/or tissue invasive CMV confirmed on histopathology.

Search methods for identification of studies

Original review (2005)

We searched the following resources without language restriction.

- The Cochrane Renal Group's Specialised Register
- The Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Database of Systematic Reviews* issue 2, 2005).
- MEDLINE (1966 to February 2005).

- EMBASE (1980 to February 2005).

The Trials Search Co-ordinator ensured that all relevant studies had been identified. Additional studies were located through article reference lists and from abstracts from international meetings.

Review update (2013)

For this update, we searched the Cochrane Renal Group's Specialised Register (to 16 January 2013) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

The Cochrane Renal Group's Specialised Register contains studies identified from:

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the specialised register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available from the Specialised Register section of information about the [Cochrane Renal Group](#).

See [Appendix 1](#) for search terms used in strategies for this review.

Data collection and analysis

This systematic review was originally undertaken by four authors (GS, JC, EH, CJ) and was published in *The Cochrane Database of Systematic Reviews* in 2005 ([Strippoli 2005](#)). This update was undertaken by five authors (DO, AW, GS, KK, EH).

Selection of studies

Two authors independently screened titles and abstracts retrieved from the searches and identified those studies that met the inclusion criteria. This process favoured over-selection in order to include all relevant studies. The full article was retrieved if uncertainty existed or when the abstract was not available. Any disagreement with article selection was resolved through discussion and consultation.

Data extraction and management

Two authors independently extracted data from eligible studies using standardised data extraction forms. Studies reported in foreign language journals were translated before data extraction. Participant characteristics (number, age, sex, co-morbidities), interventions (type of treatment, dose, duration, co-interventions) and primary and secondary outcome measures were recorded. Authors were contacted to obtain missing information on allocation concealment. Any discrepancies in data extraction were resolved in discussion. Where results of a study were published more than once, the most complete data were extracted from all sources and used in the analysis only once.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool ([Higgins 2011](#); [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - * Participants and personnel
 - * Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI). Risk differences (RD) with 95% CI were calculated for adverse effects. Continuous outcomes were calculated as mean differences (MD) with 95% CI.

Unit of analysis issues

If available, data for the first period of cross-over studies were to be included in meta-analyses; otherwise, cross-over studies were reported in the text only.

Dealing with missing data

Study authors were contacted for information on sequence generation, allocation concealments and for missing data. Where missing data were few and not thought likely to influence results, the available data were analysed.

Assessment of heterogeneity

Heterogeneity was analysed using a χ^2 test on $N-1$ degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test ([Higgins 2003](#)). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

This updated review included all studies identified in the Cochrane Renal Group's Specialised Register, which is revised regularly with published and unpublished reports identified in congress proceedings. This reduces the risk of publication bias. All reports of a single study were reviewed to ensure that all outcomes were reported to reduce the risk of selection bias.

Data synthesis

Data were pooled using a random-effects model to calculate a summary estimate of effect.

Subgroup analysis and investigation of heterogeneity

To determine whether there was any difference between study results due to plausible effect modifiers, subgroup analysis was

planned provided that sufficient numbers of studies for analysis were identified. The analysis aimed to explore the effects of patient characteristics such as type of solid organ transplanted, type of intervention, dose and duration of intervention, level of pre-existent risk, timing and methods used for diagnosis of CMV infection, time to graft loss, HHV6/7 status, and quality of study on treatment effect.

Sensitivity analysis

Where a study's results differed considerably from other studies in a meta-analysis, exclusion of the study was investigated to determine whether this altered the result of the meta-analysis.

RESULTS

Description of studies

Results of the search

The literature search for the original review consisted of a combined search of MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials (CENTRAL) and the Cochrane Renal Group's Specialised Register. There were 1930 articles identified. Of these, 1737 were excluded because they were not RCTs or were RCTs that evaluated ineligible interventions. Full-text assessment of 193 potentially eligible articles identified 10 studies (14 reports; 476 participants) ([Brennan 1997a Kidney](#); [Jung 2001 Kidney](#); [Koetz 2001 Kidney](#); [Paya 2002 Liver](#); [Queiroga 2003 Kidney](#); [Rayes 2001 Liver](#); [Sagedal 2003 Kidney](#); [Singh 2000 Liver](#); [Singh 1994 Liver](#); [Yang 1998 Kidney](#)). Four study authors responded to queries about uncertainties on study methods ([Brennan 1997a Kidney](#); [Jung 2001 Kidney](#); [Singh 2000 Liver](#); [Singh 1994 Liver](#)).

For this update, only the Cochrane Renal Group's Specialised Register was searched. This is updated continuously and contains all new kidney and related studies, reports and articles. The search identified 20 reports of nine studies. Of the nine studies, five were new studies of pre-emptive therapy versus prophylaxis ([Gerna 2008 Liver](#); [Khoury 2006 Kidney](#); [Kliem 2008 Kidney](#); [Reischig 2008 Kidney](#); [Witzke 2012 Kidney](#)). Two additional reports were identified in the search but had already been included in the original review ([Singh 1998](#); [Yang 1996](#)). A further two studies ([Qiu 2008 Kidney](#); [Tian 2005 Kidney](#)) were identified from a systematic review of RCTs conducted by [Zhang 2011](#). Further assessment of these studies, including contact with the authors facilitated through the Chinese Cochrane Centre, indicated that participants were not randomised, hence these studies were excluded. One study author responded to queries about uncertainties on study methods ([Khoury 2006 Kidney](#)).

There are three ongoing studies that are potentially relevant to this review ([NCT00372229](#); [NCT00966836](#); [NCT01552369](#)). When concluded these studies will be assessed for inclusion in a future update of this review. Another study relevant to this review was also identified for inclusion ([Scott 2011 Liver](#)), however, more information has been requested from the authors before the study can be included in meta analysis.

The combined search results are presented in [Figure 1](#).

Figure 1. Combined search results for the original and updated reviews. Reasons for exclusions are provided in text

Included studies

The combined updated study data included 1098 participants from 15 studies. Three intervention rationales were investigated by these studies.

One rationale involved randomising participants at transplant to receive viral surveillance and pre-emptive treatment on development of CMV viraemia versus prophylaxis with antiviral medications for 30 to 168 days (8 studies, 785 participants: [Gerna 2008 Liver](#); [Jung 2001 Kidney](#); [Khoury 2006 Kidney](#); [Kliem 2008 Kidney](#); [Queiroga 2003 Kidney](#); [Reischig 2008 Kidney](#); [Singh 1994 Liver](#); [Witzke 2012 Kidney](#)). (This was the only rationale in previous iterations of this review to which new study data were added for this update).

A second rationale involved randomising participants to pre-emptive treatment or to placebo or no specific therapy (6 studies, 291 participants: [Brennan 1997a Kidney](#); [Koetz 2001 Kidney](#); [Paya 2002 Liver](#); [Rayes 2001 Liver](#); [Sagedal 2003 Kidney](#); [Yang 1998 Kidney](#)). In five of these studies ([Koetz 2001 Kidney](#); [Paya 2002 Liver](#); [Rayes 2001 Liver](#); [Sagedal 2003 Kidney](#); [Yang 1998 Kidney](#)), all transplant recipients were screened for CMV viraemia. Study participants who developed viraemia were then randomised to receive pre-emptive treatment or placebo/standard care. In the study by [Brennan 1997a Kidney](#), transplant recipients were randomised at transplant to receive pre-emptive treatment (screening and treatment of those with positive viraemia) or standard care (treatment of symptomatic CMV infection when it developed). Screening occurred at the time of transplantation and at weekly intervals thereafter.

The third rational type was applied in a study by [Singh 2000 Liver](#). It investigated 22 patients who developed CMV viraemia, and were

randomised to receive oral or intravenous ganciclovir as pre-emptive treatment.

All studies investigated ganciclovir or valganciclovir. Six studies compared ganciclovir with placebo or delayed treatment ([Brennan 1997a Kidney](#); [Koetz 2001 Kidney](#); [Paya 2002 Liver](#); [Rayes 2001 Liver](#); [Sagedal 2003 Kidney](#); [Yang 1998 Kidney](#)); five compared pre-emptive ganciclovir with prophylactic ganciclovir ([Gerna 2008 Liver](#); [Jung 2001 Kidney](#); [Kliem 2008 Kidney](#); [Queiroga 2003 Kidney](#); [Singh 2000 Liver](#)); two compared pre-emptive valganciclovir with prophylactic valganciclovir ([Khoury 2006 Kidney](#); [Witzke 2012 Kidney](#)); one study compared pre-emptive valganciclovir with prophylactic valganciclovir ([Reischig 2008 Kidney](#)); and one compared pre-emptive ganciclovir with prophylactic aciclovir ([Singh 1994 Liver](#)).

Follow-up duration of all studies ranged from three to 18 months.

Excluded studies

Overall, we excluded 1976 studies. The 2005 review excluded 1916 reports, 33 reports were assessed and excluded in 2010, and 27 reports in this update. Most exclusions were made following assessment of title and abstract appraisal. The most common reasons for exclusion were for non-randomisation of participants or were for RCTs that investigated interventions outside the inclusion criteria for this review.

Risk of bias in included studies

Assessing risk of bias was problematic because many details were difficult to ascertain or not provided (see [Characteristics of included studies](#)). Study authors were contacted for clarification of study outcomes where reporting was inadequate (see [Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brennan 1997a Kidney	?	-	-	-	+	+	+
Gerna 2008 Liver	?	?	-	-	+	-	+
Jung 2001 Kidney	?	?	-	-	+	+	?
Khoury 2006 Kidney	+	+	-	-	+	+	-
Kliem 2008 Kidney	+	+	-	-	+	+	-
Koetz 2001 Kidney	?	?	?	?	+	-	?
Paya 2002 Liver	+	+	+	?	+	-	-
Queiroga 2003 Kidney	?	?	-	-	+	-	?
Rayes 2001 Liver	?	?	-	-	+	+	?
Reischig 2008 Kidney	+	?	-	-	+	+	+
Sagedal 2003 Kidney	?	?	-	-	+	+	-

Figure 3. (Continued)

Neisberg 2000 Kidney	+	+	-	-	+	+	+
Sagedal 2003 Kidney	?	?	-	-	+	+	-
Singh 1994 Liver	+	?	-	-	+	-	?
Singh 2000 Liver	?	?	-	-	+	-	?
Witzke 2012 Kidney	?	+	-	-	+	+	-
Yang 1998 Kidney	?	?	-	-	+	-	+

Allocation

Allocation concealment was considered to be at low risk of bias in four studies (Khoury 2006 Kidney; Kliem 2008 Kidney; Paya 2002 Liver; Witzke 2012 Kidney); while the remaining studies did not report methods used to conceal the randomisation process.

Risk of bias in random sequence generation bias was considered low in five studies (Khoury 2006 Kidney; Kliem 2008 Kidney; Paya 2002 Liver; Reischig 2008 Kidney; Singh 1994 Liver). While the majority of other papers reported randomisation of patients, the method used to generate a random sequence was not reported. The risk of bias in random sequence generation was high in one study (Brennan 1997a Kidney) (last digit of medical number).

Blinding

Blinding of participants and personnel was reported in Koetz 2001 Kidney and Paya 2002 Liver. However, only Paya 2002 Liver provided detailed information to indicate that the study was at low risk of performance bias. Neither study reported blinding or provided information on whether outcome assessors were blinded to intervention groups. Of the 15 included studies, five (Gerna 2008 Liver; Kliem 2008 Kidney; Reischig 2008 Kidney; Sagedal 2003 Kidney; Witzke 2012 Kidney) were reported to be open-label. These, and the remaining eight studies, were assessed as being at high risk of bias for performance and detection bias because interpretation of the clinical outcome of CMV disease by clinical features could be affected by lack of blinding of participants, investigators and outcome assessors.

Incomplete outcome data

Brennan 1997a Kidney had missing outcome data due to losses to follow-up. However, this was considered unlikely to influence the results of this study. Bias due to incomplete outcome data was considered low for all other studies.

Selective reporting

Bias through selective reporting was considered a low risk in eight studies (Brennan 1997a Kidney; Jung 2001 Kidney; Khoury 2006 Kidney; Kliem 2008 Kidney; Rayes 2001 Liver; Reischig 2008 Kidney; Sagedal 2003 Kidney; Witzke 2012 Kidney). In the remaining seven, selective reporting bias was considered high as they did not report outcomes of importance for this review. In the study of Gerna 2008 Liver graft loss, adverse effects and opportunistic infections were not reported. In the studies by Koetz 2001 Kidney and Yang 1998 Kidney all-cause mortality, graft loss and acute rejection were not reported. In Paya 2002 Liver, all-cause mortality and graft loss were not reported. Acute rejection was not reported in either Queiroga 2003 Kidney or Singh 1994 Liver, and Singh 2000 Liver did not report graft loss or acute rejection.

Other potential sources of bias

Five studies reported pharmaceutical sponsorship (Khoury 2006 Kidney; Kliem 2008 Kidney; Paya 2002 Liver; Sagedal 2003 Kidney; Witzke 2012 Kidney) and were judged as high risk of bias. Several other studies reported sponsorship from educational and government organisations (Brennan 1997a Kidney; Gerna 2008 Liver; Reischig 2008 Kidney; Yang 1998 Kidney). These studies were considered to be at low risk of bias. The remaining studies did not state any form of sponsorship and their risk of bias was unclear (Jung

2001 Kidney; Koetz 2001 Kidney; Queiroga 2003 Kidney; Rayes 2001 Liver; Singh 1994 Liver; Singh 2000 Liver).

Effects of interventions

See: **Summary of findings for the main comparison** Pre-emptive medication for cytomegalovirus (CMV) viraemia compared to placebo/no treatment to prevent CMV disease in solid organ transplant recipients; **Summary of findings 2** Pre-emptive medication compared to prophylaxis for cytomegalovirus (CMV) viraemia to prevent CMV disease in solid organ transplant recipients

Pre-emptive treatment for CMV infection versus placebo or standard care

There were 1393 patients screened for entry to the six studies of pre-emptive treatment versus placebo or standard care. Of these, 1035 patients were excluded (no CMV viraemia in 597, CMV viraemia below threshold for study entry in 116, other reasons in 322) so that 358 patients were eligible for study entry. However, 64 patients (17.8%) developed CMV disease within the 0 to 10 day time gap between testing for viraemia and randomisation, and thus were excluded. The proportion of patients in each study who developed CMV disease before CMV viraemia was detected varied from 0% to 32%. In addition, six (1.7%) other patients were excluded after randomisation for protocol violations, so that 288 patients were evaluated.

Compared with placebo or standard care, pre-emptive treatment significantly reduced the risk of CMV disease (Analysis 1.1 (6 studies, 288 participants): RR 0.29, 95% CI 0.11 to 0.80). The heterogeneity ($I^2 = 54\%$, $P = 0.06$) was explained by the study undertaken by Brennan 1997a Kidney, which was the only study in which transplant recipients were randomised to screen (and treat) for CMV viraemia versus no screening, rather than randomising participants with CMV viraemia to treatment or not. Removing this study resulted in homogenous results ($I^2 = 0\%$, $P = 0.54$). There was no significant difference for the outcome of CMV disease in studies that used oral ganciclovir compared with studies that used intravenous ganciclovir preparations ($P = 0.93$ for interaction).

For the outcomes of CMV organ involvement (Analysis 1.2 (5 studies, 217 participants): RR 0.41, 95% CI 0.06 to 2.63) or CMV associated symptoms (Analysis 1.3 (5 studies, 217 participants): RR 0.28, 95% CI 0.06 to 1.21), the summary estimates favoured treatment, but the CIs were wide. There was also no significant difference in the risks of acute rejection (Analysis 1.4 (3 studies, 185 participants): RR 1.21, 95% CI 0.69 to 2.12), all-cause mortality (Analysis 1.5.1 (3 studies, 176 participants): RR 1.23, 95% CI 0.35 to 4.30), graft loss (Analysis 1.5.2 (1 study, 36 participants): 0.28, 95% CI 0.01 to 5.35), leucopenia (Analysis 1.7.1 (2 studies, 114 participants): RR 1.54, 95% CI 0.16 to 15.36), or kidney dysfunction (Analysis 1.7.2 (1 study, 36 participants): RR 0.93, 95% CI 0.18 to 4.92). There was no significant variation in treatment effect for any these outcomes when studies that used oral and intravenous ganciclovir regimens were considered separately.

Pre-emptive treatment for CMV viraemia versus anti-viral prophylaxis

Symptomatic CMV disease occurred at rates between 0% and 28.7% in the pre-emptive group and 0% and 29.2% in the prophylaxis group. The risk of developing CMV disease was not significant-

ly different among groups ([Analysis 2.1](#) (7 studies, 753 participants): RR 1.02; 95% CI 0.43 to 2.44).

There was considerable heterogeneity among the seven studies ($I^2 = 67\%$). Of these, two favoured pre-emptive therapy and two favoured prophylaxis. Removal of studies by [Khouri 2006 Kidney](#) and [Singh 1994 Liver](#) from the analysis, which both favoured pre-emptive therapy, decreased heterogeneity considerably ($I^2 = 26\%$) and a clinically significant result favouring prophylaxis was observed (5 studies, 608 participants: RR 2.19, 95% CI 1.3 to 4.23). Investigation of the [Singh 1994 Liver](#) study indicated that an inferior agent (aciclovir) was used in the prophylaxis arm compared with a superior agent (ganciclovir) in the pre-emptive arm ([Hodson 2013](#)) which may have exerted a favourable influence on pre-emptive treatment. Investigation of the [Khouri 2006 Kidney](#) study did not yield any substantial differences to account for the reduction in heterogeneity.

It was found that alternately excluding the two studies ([Kliem 2008 Kidney](#); [Witzke 2012 Kidney](#)) that favoured prophylaxis, the relative risk supported pre-emptive therapy, although the result was not significant (5 studies, 319 participants: RR 0.42; 95% CI 0.16 to 1.11).

CMV infection was significantly more common in the pre-emptive group compared with the prophylaxis group ([Analysis 2.2](#) (7 studies, 727 participants): RR 2.06, 95% CI 1.44 to 2.96). However, there was considerable heterogeneity ($I^2 = 71\%$).

There was no significant difference observed between the pre-emptive and prophylaxis groups for all-cause mortality ([Analysis 2.3.1](#) (7 studies, 753 participants): RR 1.19, 95% CI 0.56 to 2.51), graft loss ([Analysis 2.3.2](#) (7 studies, 753 participants): RR 1.07, 95% CI 0.41 to 2.82), and acute rejection ([Analysis 2.4](#) (6 studies, 693 participants): RR 1.23, 95% CI 0.75 to 2.03). No heterogeneity existed among the studies for all-cause mortality. Some degree of heterogeneity existed in the graft loss analysis ($I^2 = 41\%$) and acute rejection ($I^2 = 44\%$) analyses. Heterogeneity was considerably diminished ($I^2 = 14\%$) in the graft loss analysis when [Jung 2001 Kidney](#) was excluded. The only differences observed between [Jung 2001 Kidney](#) and all other studies were a later start for prophylaxis and a higher dose of oral ganciclovir (3000 mg/d compared with 1500 mg to 2000 mg/d).

Heterogeneity was abolished entirely in the acute rejection analysis when the study by [Witzke 2012 Kidney](#) was excluded from the analysis. The only difference that existed between the [Witzke 2012 Kidney](#) study and others was the non-inclusion of high risk transplant recipients (D+/R-).

No significant difference was identified between pre-emptive therapy and prophylaxis for infections other than CMV including bacterial ([Analysis 2.5.1](#) (2 studies, 168 participants): RR 0.89, 95% CI 0.55 to 1.43), viral ([Analysis 2.5.2](#) (1 study, 70 participants): RR 1.57, 95% CI 0.92 to 2.70), and fungal infections ([Analysis 2.5.3](#) (1 study, 70 participants): RR 1.89, 95% CI 0.18 to 19.89).

Leucopenia was significantly less common in patients who underwent pre-emptive therapy compared with prophylaxis ([Analysis 2.6.1](#) (6 studies, 729 participants): RR 0.42, 95% CI 0.20 to 0.90). Some heterogeneity existed among the studies ($I^2 = 45\%$) which was considerably diminished when the [Kliem 2008 Kidney](#) study was excluded from the analysis ($I^2 = 15\%$). No identifiable differences in the [Kliem 2008 Kidney](#) study were observed in compari-

son with others in this subgroup analysis. No significant difference was observed for neurological dysfunction between the therapies ([Analysis 2.6.2](#) (3 studies, 187 participants): RR 0.58, 95% CI 0.17 to 1.96).

In general, other adverse effects were poorly reported in eight pre-emptive therapy versus prophylaxis studies; one study ([Reischig 2008 Kidney](#)) provided most of the data ([Analysis 2.6](#)).

Serostatus stratification of CMV disease was reported in two studies ([Khouri 2006 Kidney](#); [Reischig 2008 Kidney](#)). No significant differences in symptomatic CMV disease or CMV infection were observed between pre-emptive treatment and prophylaxis for high risk transplant recipients (D+/R-) ([Analysis 2.7](#)). For lower risk transplant recipients (D+ or D-/R+), there was no significant difference in symptomatic CMV disease ([Analysis 2.8.1](#)) but CMV infection was significantly less common in recipients receiving prophylaxis ([Analysis 2.8.2](#) (2 studies, 129 participants): RR 2.07, 95% CI 1.25 to 3.42).

Oral versus intravenous ganciclovir for pre-emptive treatment of CMV viraemia

We found that 22/72 (31%) liver transplant recipients undergoing surveillance developed CMV viraemia and entered a study comparing oral and intravenous ganciclovir for pre-emptive treatment ([Singh 2000 Liver](#)). There were no significant differences in the risk of CMV disease ([Analysis 3.1](#)), all-cause mortality ([Analysis 3.2](#)) or other infections ([Analysis 3.3](#)) between the regimens.

Other outcomes

No data were available on the outcomes of death due to CMV disease. The time to development of CMV disease outcome was reported in four studies ([Gerna 2008 Liver](#); [Khouri 2006 Kidney](#); [Kliem 2008 Kidney](#); [Reischig 2008 Kidney](#)). Moreover, the different methods of measurement used to report these outcomes (median, mean and frequencies) prevented meta-analysis.

Subgroup analyses according to organ transplanted, antiviral medication, duration of treatment, timing and methods used for diagnosis of CMV infection, time to graft loss, HHV6/7 status or methodological quality were not possible because of the small number of studies and enrolled patients.

DISCUSSION

Summary of main results

This review identified eight studies that compared pre-emptive with prophylactic therapy (784 patients) and six studies that compared pre-emptive therapy versus placebo or standard care (288 patients) where the primary outcome was CMV disease. Tests and thresholds used to detect CMV viraemia were different across the studies, but results were generally consistent. Confidence intervals were wide across most outcomes, indicating considerable imprecision ([Summary of findings for the main comparison](#); [Summary of findings 2](#)). Fewer patients were evaluated for other outcomes, and CIs around observed treatment effects were so wide that other benefits (or harms) of pre-emptive therapy could not be excluded.

Pre-emptive treatment using standard detection methods for CMV viraemia was 71% more effective than placebo or standard care in reducing the risk of CMV disease (RR 0.29, 95% CI 0.11 to 0.80). CMV organ involvement was 59% lower in the pre-emptive therapy regime compared with the placebo/standard care regime. Howev-

er, the quality of evidence was low due to small patient numbers and lack of blinding across all studies. No significant differences in the risks of all-cause mortality, acute rejection, graft loss, other infections, leucopenia, or kidney dysfunction were demonstrated between pre-emptive therapy and placebo or standard care ([Summary of findings for the main comparison](#)).

There was no significant difference in preventing CMV disease using pre-emptive versus prophylactic therapy. However, there was significant heterogeneity among studies so that superiority of one or other treatment could not be excluded. The major benefit observed for pre-emptive therapy was a 58% reduction in leucopenia compared with prophylaxis, while other adverse effects did not differ significantly, or were not reported. There were no significant differences in the risks of all-cause mortality, graft loss, acute rejection and infections other than CMV. There was also no significant difference observed between pre-emptive therapy and prophylaxis with regards to CMV disease in high risk solid organ transplant patients (D+/R-) ([Summary of findings 2](#)).

Only one study of oral versus IV pre-emptive regimens was included in this review; it showed no significant difference in the risk of CMV disease between the groups.

It should be emphasised that oral ganciclovir, which was the basis for three of the included analyses, is no longer available and has been replaced by valganciclovir.

Overall completeness and applicability of evidence

Overall, the evidence from the 15 studies included in this review prevented confident conclusions to be made on the efficacy of pre-emptive therapy in preventing CMV disease, graft loss, acute rejection and all-cause mortality in comparison with placebo/no specific treatment or with prophylaxis. This was primarily due to a lack of adequately powered studies and low precision of the measured outcomes. There was also a lack of studies that compared pre-emptive therapy across a broad range of different transplanted organs; the highest representation was for kidney transplant recipients among the 15 studies included in this review.

Many studies did not address important outcomes, including adverse effects of medications. In contrast, the evidence base for routine prophylaxis compared with placebo/no specific therapy is substantial, arising from 19 studies of 1981 participants ([Hodson 2005](#); [Hodson 2013](#)) which enabled more precise results to be derived.

Prophylaxis has been shown to reduce CMV disease by about 60% (RR = 0.42), with tight CIs (0.34 to 0.52), strong evidence of statistically significant benefit ($P < 0.0001$), and considerable homogeneity of results across all studies ($I^2 = 13\%$, where only one of the point estimates of the 19 studies did not favour prophylaxis ([Hodson 2005](#); [Hodson 2013](#)).

Antiviral prophylaxis has been shown to reduce CMV-related mortality, all-cause mortality, and clinically important disease caused by opportunistic infections.

Although both prophylaxis ([Hodson 2013](#)) and pre-emptive therapy significantly reduce CMV disease compared with placebo or no specific therapy in solid organ transplant recipients, this review has demonstrated that the available data evaluating pre-emptive therapy (6 studies; 288 participants) was of low quality (GRADE) com-

pared with the high quality data (GRADE) evaluating antiviral prophylaxis (19 studies; 1981 participants).

There appeared to be little evidence that the use of medications now considered to be less effective than valganciclovir or ganciclovir ([Humar 2009](#); [Pescovitz 2007](#)) influenced the results in studies comparing pre-emptive therapy with prophylaxis. Two studies (117 participants) of eight studies used aciclovir ([Singh 1994 Liver](#)) or valaciclovir ([Reischig 2008 Kidney](#)) in the prophylaxis arm of the studies. This would potentially favour pre-emptive therapy and could have contributed to the results of the [Singh 1994 Liver](#) study. All studies comparing pre-emptive therapy with placebo or no specific therapy used ganciclovir, which has been superseded by valganciclovir for prophylaxis or pre-emptive therapy. RCT data have shown no significant difference in efficacy for prophylaxis of CMV disease between ganciclovir and valganciclovir ([Hodson 2005](#)) so it can be presumed that valganciclovir would be more effective than placebo in prophylaxis or pre-emptive therapy studies, although this has not been formally tested in RCTs.

There was also substantial difference among studies with regard to CMV surveillance testing. The type of test used (pp65 antigenaemia assay or PCR DNA), the assays used, the frequency of surveillance (weekly to monthly), the cut-off values (DNA PCR > 400 to > 2000 copies/mL) to define CMV infection and the blood component used for testing were factors contributing to these differences. This large variability among studies further reduced confidence of drawing definite conclusions about the applicability of pre-emptive therapy for several reasons. Longer time intervals between surveillance tests potentially increases the chances of CMV infection not being detected so that the patient develops CMV disease before he or she can be entered in a study. This means that the proportion of preventable CMV disease patients in the pre-emptive arm may have erroneously increased. Lower cut-off values used for diagnosing CMV infection with more frequent testing could result in earlier detection of CMV infection and enable earlier initiation of therapy to prevent CMV disease and reduce the effects of indirect CMV infection. Alternatively, higher cut-off values with longer periods between tests could result in delayed therapy and potentially increase the number of preventable CMV disease cases. Finally, PCR testing needs consideration as to what component of blood is being tested; whole blood will often yield higher rates of CMV DNA compared to plasma ([Humar 2009](#)).

Quality of the evidence

This systematic review identified 15 studies of 1094 participants; of these, 784 participants were evaluated in studies that compared pre-emptive therapy with prophylaxis; and 288 were evaluated in studies that compared pre-emptive therapy with placebo/no specific treatment. The 15 studies failed to report all relevant outcomes, were frequently at high risk of bias, demonstrated imprecision and heterogeneity among studies which lowered the integrity of the meta-analysed results.

The poorly reported methods of randomisation and allocation concealment have prevented an accurate assessment of the risk of selection bias: only three studies adequately performed both. The lack of allocation concealment in these studies introduced the potential to overestimate outcome benefits ([Hewitt 2005](#)). The blinding of outcome assessors and personnel was poorly performed in most studies; only one reported blinding of participants and investigators. The blinding of outcome assessors was not conducted in

any study because all study authors were judged to also be outcome assessors. Therefore, most included studies were at high risk of both performance and detection bias. The risk of attrition bias was considered to be low in all studies. Half of the studies did not include outcomes that were assessed to be important by the review authors.

Pre-emptive therapy compared with placebo/no specific therapy significantly reduced CMV disease (RR 0.29, 95% CI 0.11 to 0.80). However, CIs were wide (0.11 to 0.80), statistical significance was moderate ($P = 0.02$), and there was evidence of significant heterogeneity among studies ($I^2 = 54\%$): two studies favoured pre-emptive therapy and two large studies favoured prophylaxis. Similarly, no significant difference was identified in the risk for CMV disease between pre-emptive therapy and prophylaxis (RR 1.02, 95% CI 0.43 to 2.44); CIs were wide, indicating considerable imprecision, and there was significant heterogeneity ($I^2 = 63\%$).

Data for outcomes other than CMV disease were more limited. Particularly, we found that there was failure to report outcomes relating to adverse effects. We also found that low participant numbers and few events increased imprecision.

Only two studies stratified CMV disease and infection by the high risk serostatus D+/R- (Khouri 2006 Kidney; Reischig 2008 Kidney). Only 49 patients were available from these two studies which prevented comprehensive analysis. Such subset analysis required a larger sample size to enable accurate assessment of this high risk group.

Overall, the quality of the evidence was considered to be low or very low because of small numbers of enrolled participants, few events, significant heterogeneity, lack of blinding, and inadequate allocation concealment (Summary of findings for the main comparison; Summary of findings 2).

Potential biases in the review process

The search criteria, analysis, and data extraction were performed to a high standard (see Methods). Four reviewers independently performed the analysis and data extraction; any conflict was resolved by an independent party. This further decreased the risk of bias for the review. The search strategy for the review was thorough. The Cochrane Renal Group's Specialised Register includes complete listings of current studies and is regularly updated to include new studies and additional reports of existing studies from journals and conference reports.

It is possible that some studies may have been missed where the study report has only been published in abstract form in conference proceedings, which have not yet been handsearched.

Overall, this review and review search represent an up-to-date assessment of current pre-emptive therapy studies.

Agreements and disagreements with other studies or reviews

Zhang 2011 conducted a systematic review comparing pre-emptive therapy and prophylaxis in solid organ transplants, and consistent with our review findings, also found no significant difference in the risk of CMV disease, graft loss, acute rejection and mortality between pre-emptive therapy and prophylaxis. However, our review identified a 58% reduced risk of leucopenia in the pre-emptive ther-

apy rationale which was not identified by Zhang 2011. The studies included in this review for pre-emptive treatment versus prophylaxis were mostly the same as those analysed by Zhang 2011; the exceptions were two Chinese studies included by Zhang 2011 that were excluded from our review on the basis that they were not RCTs (Qiu 2008 Kidney; Tian 2005 Kidney). Zhang 2011 did not include either the Gerna 2008 Liver transplant study in children or the liver transplant study by Singh 1994 Liver which were included in this review. This would account for numerical variations between these reviews, although much of the statistical outcomes remain the same.

A recent commentary on CMV in solid organ transplant recipients also suggested the need for more studies comparing pre-emptive therapy with prophylaxis to identify if pre-emptive therapy may increase the risk of the indirect effects of CMV infection (Humar 2009). This is in agreement with our findings where several studies did not report on outcomes relating to indirect effects of CMV infection. Our findings are consistent with recent guidelines from the British Transplantation Society (BTS 2011), Kidney Disease Improving Global Outcomes (KDIGO 2009) and Caring for Australians with Renal Impairment (CARI 2010). A summary of these guidelines are presented in Table 1.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review identified no significant differences in efficacy between pre-emptive therapy and prophylaxis for preventing CMV disease, graft loss, and death in solid organ transplant recipients. However, study data remain sparse. The ability to ascertain true benefits and harms remains problematic when compared with prophylaxis due to heterogeneity between study results together with low sample sizes and event rates leading to imprecision.

Pre-emptive therapy has shown benefits over placebo and standard care. This review has identified an increased risk of CMV infection with pre-emptive therapy, which may have deleterious impacts on the indirect effects of CMV infection including graft loss, acute rejection, and infections other than CMV compared with prophylaxis. While no significant differences in meta-analyses could be demonstrated for these outcomes, heterogeneity around the results indicate that differences cannot be excluded. Furthermore, four year follow-up data reported by Reischig 2008 Kidney suggest that graft loss may be higher in patients treated with prophylaxis compared with pre-emptive therapy. Four year follow-up data for the much larger Witzke 2012 Kidney study are awaited.

This review highlights the need to standardise testing frequency and cut off levels for positive tests used in the surveillance testing for CMV infection which could reduce variability between institutions and in studies. A standardised method should test patients frequently (especially within the first six months post-transplant) and should have a low threshold for detection. The results should be immediately available to enable therapy to be commenced as soon as possible after the surveillance threshold is exceeded.

Implications for research

In view of the heterogeneity of results in currently available studies, further well designed and adequately powered studies are required to compare three or more months of prophylactic therapy using an anti-CMV viral medication with pre-emptive therapy for patients

who develop viraemia. Such studies should be powered to enable assessment of direct and indirect effects of CMV infection, adverse effects of medications and resource utilisation have sufficient follow-up to assess graft loss and mortality, and include standardised thresholds and frequency of testing for CMV viraemia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Brennan 1997a Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 12.3 to 18.2 months
Participants	<ul style="list-style-type: none"> Country: USA Setting: University CMV status: D/R+; D+/R- Kidney transplant recipients: 1st transplant (48); 2nd transplant (3) Number: 39 Mean age $\pm$ SD: treatment group (48 $\pm$ 2.6 years); control group (47 $\pm$ 3.2 years)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive IV ganciclovir 5 mg/kg every 12 hours for 3 weeks <p>Control group</p> <ul style="list-style-type: none"> Deferred ganciclovir (same schedule)
Outcomes	<ol style="list-style-type: none"> CMV disease Acute rejection All-cause mortality Graft loss Adverse events
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: qualitative PCR for CMV DNA; shell vial culture; serology

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified

Brennan 1997a Kidney (Continued)

Allocation concealment (selection bias)	High risk	Authors reported that patients allocated according to last digit of medical record number (odd and even numbers)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as some patients received IV medications while other received no treatment. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients excluded but this was unlikely to influence results
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported
Other bias	Low risk	Supported by grant from Missouri Kidney Program

Gerna 2008 Liver

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 24 months
Participants	<ul style="list-style-type: none"> Country: Italy Setting: NS CMV status: D+/R+, D+/R- Paediatric liver transplant patients Number: 21 Median age; range: treatment group (11 months; 2 months to 11 years); control group (19 months; 6 months to 6 years)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive ganciclovir 5 mg/kg twice/d when positive CMV DNAemia occurred <p>Control group</p> <ul style="list-style-type: none"> Prophylactic ganciclovir 5 mg/kg twice/d for 30 days then pre-emptive IV ganciclovir 5 mg/kg twice/d when positive CMV DNAemia occurred
Outcomes	<ol style="list-style-type: none"> CMV infection Acute rejection Time to development of CMV
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: qualitative PCR for CMV DNA >100,000 copies/mL for pre-emptive therapy; viral assay pp65-antigenaemia for prophylaxis

Risk of bias

Bias	Authors' judgement	Support for judgement
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Gerna 2008 Liver (Continued)

Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open labelled and the interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome was likely dependent on the study investigators as the study was open labelled.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	All outcomes specified in methods were reported; however, outcomes of interest were not reported: graft loss, graft function, adverse effects of medications and other infections
Other bias	Low risk	Trial stopped early due to ethical reasons. No significant difference between the groups led to the conclusion that prophylactic treatment of patients would be unethical due to unjustified treatment.

Jung 2001 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 12 months
Participants	<ul style="list-style-type: none"> Country: Germany Setting: NS CMV status: D/R+, D+/R-, D-/R- Kidney transplant recipients (1st transplant only) Number: 70 Mean age: NS
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive oral ganciclovir 3000 mg/d for 14 days or until test negative <p>Control group</p> <ul style="list-style-type: none"> Prophylactic oral ganciclovir 3000 mg/d for 90 days starting at week 2 after transplant
Outcomes	<ol style="list-style-type: none"> CMV disease CMV infection Acute rejection All-cause mortality Graft loss Adverse events

Jung 2001 Kidney (Continued)

Notes	Method for detection of CMV infection: pp65 antigenaemia > 2 positive cell/20 x 10⁴; PCR for CMV DNA > 400 copies/mL⁵

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as no placebo was given to the pre-emptive group. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators and assessment of the outcome could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported
Other bias	Unclear risk	No sponsorship of trial was stated

Khoury 2006 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 12 months
Participants	<ul style="list-style-type: none"> Country: USA Setting: University CMV status: D/R+, D+/R-, D-/R- Kidney transplant recipients Number: 99 Mean age ± SD: treatment group (47.5 ± 14.96 years); control group (51.9 ± 13.91 years)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive oral valganciclovir 900 mg twice/d for at least 21 days or until test negative <p>Control group</p> <ul style="list-style-type: none"> Prophylactic oral valganciclovir 900 mg/d for 100 days after transplantation
Outcomes	<ol style="list-style-type: none"> CMV disease CMV infection All-cause mortality Graft loss

Khoury 2006 Kidney (Continued)

5. Other infections
6. Acute rejection
7. Pharmacoeconomics
8. Time to development of CMV

Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: quantitative PCR on whole blood for CMV DNAemia with a cut off value of > 2000 copies/mL
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by computer program with 1:1 block design
Allocation concealment (selection bias)	Low risk	Clinical pharmacist allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as pre-emptive group was not given placebo. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported and all outcomes of importance were included
Other bias	High risk	Roche supplied research support and the antiviral medication

Kliem 2008 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 48 months
Participants	<ul style="list-style-type: none"> Country: Germany Setting: Multicentre CMV status: D/R+, D+/R-, D-/R- Kidney transplant recipients Number: 148 Mean age $\pm$ SD: treatment group (50.9 $\pm$ 12.4 years); control group (48.3 $\pm$ 12.4 years)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive IV ganciclovir 5 mg/kg twice/d for at least 10 days or until test was < 100 copies CMV DNA/mL on two successive tests <p>Control group</p>

Kliem 2008 Kidney (Continued)

- Prophylactic oral ganciclovir 1000 mg/d for 90 days within 48 hours following transplantation (for those who could not tolerate oral therapy temporary prophylaxis was provided as ganciclovir 5 mg/kg twice daily)

Outcomes	<ol style="list-style-type: none"> 1. CMV disease 2. CMV infection 3. All-cause mortality 4. Graft loss 5. Acute rejection 6. Graft function 7. Adverse events 8. Time to development of CMV
Notes	<ul style="list-style-type: none"> • Method for detection of CMV infection: quantitative PCR on whole blood for CMV DNAemia with a cut off value of > 400 copies/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised to either treatment group centrally by phone
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open labelled. The interpretation of clinical symptoms could be influenced by blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported, however, outcome of infections not reported, however, it is unlikely that this would affect study outcome
Other bias	High risk	<p>Support from Roche Pharma AG</p> <p>Authors; Kliem, Fricke, Burg and Radermacher received honoraria for speaking and providing advice to Roche Pharma AG</p>

Koetz 2001 Kidney

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Follow-up period: 3 months
Participants	<ul style="list-style-type: none"> • Country: Germany • Setting: University • CMV status: D/R+, D+/R-

Koetz 2001 Kidney (Continued)

- Kidney and liver transplant recipients
- Number: 12
- Mean age: NS

Interventions	Treatment group <ul style="list-style-type: none"> • Pre-emptive IV ganciclovir 2 x 5 mg/kg/d for 2 weeks Control group <ul style="list-style-type: none"> • Placebo: 0.9% NaCl for 2 weeks
Outcomes	1. CMV disease and syndrome
Notes	<ul style="list-style-type: none"> • Method for detection of CMV infection: pp65 antigenaemia > 5 positive cells/20 x 10⁴

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors reported study as double blind but did not state methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported and unclear whether outcome assessors were blinded to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	All outcomes specified in methods were reported; however, outcomes of interest not reported included death, graft loss, graft function and acute rejection
Other bias	Unclear risk	No sponsorship of trial was stated

Paya 2002 Liver

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Follow-up period: 4 months
Participants	<ul style="list-style-type: none"> • Country: USA • Setting: University • CMV status: D/R+, D+/R- • Liver transplant recipients (1st transplant only) • Number: 69 • Median age; range: treatment group (54 years; 23 to 67 years); control group (50 years; 26 to 67 years)

Paya 2002 Liver (Continued)

Interventions	Treatment group <ul style="list-style-type: none"> Pre-emptive oral ganciclovir 1000 mg 3 times daily for 8 weeks Control group <ul style="list-style-type: none"> Placebo
Outcomes	1. CMV disease 2. Acute rejection 3. Other infections
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: qualitative PCR for CMV DNA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred via predetermined randomisation chart
Allocation concealment (selection bias)	Low risk	Allocation performed by unblinded pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel were blinded and oral placebo treatment was visually identical to oral ganciclovir
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported and unclear whether outcome assessors were blinded to treatment groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	Outcomes of interest not reported: Death and graft loss
Other bias	High risk	Roche pharmaceuticals supplied oral ganciclovir

Queiroga 2003 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 6 months
Participants	<ul style="list-style-type: none"> Country: Brazil Setting: NS CMV status: D/R+, D+/R-, D-/R- Kidney transplant recipients Number: 34 Mean age: NS
Interventions	Treatment group

Queiroga 2003 Kidney (Continued)

- Pre-emptive oral ganciclovir (dose/route not specified)

Control group

- Ganciclovir 750 g 3 times/d for 90 days

Outcomes	<ol style="list-style-type: none"> 1. CMV disease 2. CMV infection 3. All-cause mortality 4. Graft loss
Notes	<ul style="list-style-type: none"> • Method for detection of CMV infection: pp65 antigenaemia > 3 positive cell/30 x 10⁴

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as placebo was not given to pre-emptive group. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	All outcomes specified in methods were reported; however, acute rejection was not reported
Other bias	Unclear risk	No sponsorship of trial was stated

Rayes 2001 Liver

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Follow-up period: 4 months
Participants	<ul style="list-style-type: none"> • Country: Germany • Setting: University • CMV status: D/R+, D+/R-, D-/R- • Liver transplant recipients • Number: 60 • Mean age ± SE: treatment group (53 ± 2 years); control group (49 ± 2 years)
Interventions	Treatment group

Rayes 2001 Liver (Continued)

- Pre-emptive oral ganciclovir 1000 mg x 3 times/d for 14 days

Control group

- No treatment (treatment given when CMV disease presented)

Outcomes	<ol style="list-style-type: none"> 1. CMV disease and syndrome 2. CMV infection 3. Acute rejection 4. Adverse events 5. All-cause mortality
Notes	<ul style="list-style-type: none"> • Method for detection of CMV infection: pp65 antigenaemia > 1 positive cell/1 x 10⁴; qualitative PCR for CMV DNA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different treatment schemes oral versus intravenous therefore not blinded. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported and all outcomes of importance were included
Other bias	Unclear risk	No sponsorship of trial was stated

Reischig 2008 Kidney

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Primary follow-up period: 12 months. 4 year follow-up data
Participants	<ul style="list-style-type: none"> • Country: Czech Republic • Setting: University • CMV status: D/R+, D+/R-, D-/R- • Kidney transplant recipients • Number: 70 • Mean age ± SD: treatment (50 ± 13 years); control group: 48 ± 12 years)

Reischig 2008 Kidney (Continued)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive oral valganciclovir 900 mg twice/d for at least 14 days or until test negative <p>Control group</p> <ul style="list-style-type: none"> Prophylactic oral valaciclovir 2 g 4 times/d for 3 months starting 1 to 7 days post transplantation
Outcomes	<ol style="list-style-type: none"> CMV disease CMV infection All-cause mortality Graft loss Other infections Acute rejection Time to development of CMV Adverse events
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: quantitative PCR on whole blood for CMV DNAemia with a cut off value of > 2000 copies/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred 1:1 to either group via a random number table
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open labelled. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported and all outcomes of importance were included
Other bias	Low risk	Study was supported by an award from the Ministry of Education, Youth and Physical Training of the Czech Republic

Sagedal 2003 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 12 months
Participants	<ul style="list-style-type: none"> Country: Norway Setting: University

Sagedal 2003 Kidney (Continued)

- CMV status: D/R+, D+/R-
- Kidney transplant recipients (1st transplant only)
- Number: 80
- Mean age; range: treatment group (55 years; 22 to 79); control group (56 years; 21 to 78)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Pre-emptive oral ganciclovir 100 mg x 3 times/d (duration not specified) <p>Control group</p> <ul style="list-style-type: none"> • No treatment
Outcomes	<ol style="list-style-type: none"> 1. CMV syndrome and disease 2. Acute rejection 3. All-cause mortality 4. Serum creatinine
Notes	<ul style="list-style-type: none"> • Method for detection of CMV infection: pp65 antigenaemia > 1 positive cell/10 x 10⁴

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-labelled. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Infection other than CMV were not reported past 12 weeks, however, this would not affect the study outcomes
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported and all outcomes of importance were included
Other bias	High risk	<p>Trial was supported by grants from the Research Council of Norway and Hoffmann-La Roche, Norway</p> <p>Ganciclovir was supplied by F. Hoffmann La-Roche AG</p>

Singh 1994 Liver

Methods	<ul style="list-style-type: none"> • Study design: parallel RCT • Follow-up period: 6 months
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Singh 1994 Liver (Continued)

Participants	<ul style="list-style-type: none"> Country: USA Setting: University CMV status: D/R+, D+/R-, D-/R- Liver transplant recipients: 1st transplant (44); 2nd transplant (3) Number: 47 Mean age; range: treatment group (49 years; 22 to 66); control group (45 years; 21 to 69)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive IV ganciclovir 5 mg/kg twice/d x 7 days <p>Control group</p> <ul style="list-style-type: none"> Oral acyclovir 800 mg x 4 times/d x 24 weeks
Outcomes	<ol style="list-style-type: none"> CMV syndrome and disease All-cause mortality Graft loss Adverse events
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: shell vial culture; EIA (titre > 0.79 positive)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by CMV serostatus of donor and recipient. Randomisation process by blocks of 4
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, however, different medications and administration routes were used therefore it was considered not to be blinded. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	All outcomes specified in methods were reported; however, acute rejection was not reported
Other bias	Unclear risk	No sponsorship of trial was stated

Singh 2000 Liver

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 3 months
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Singh 2000 Liver (Continued)

Participants	<ul style="list-style-type: none"> Country: USA Setting: University CMV status: D/R+, D+/R-, D-/R- Liver transplant recipients Number: 22 Mean age: Treatment group (50.9 years); control group (49.9 years)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Pre-emptive oral ganciclovir 2000 mg 3 times/d for 2 weeks, then 1000 mg 3 times/d for 4 weeks <p>Control group</p> <ul style="list-style-type: none"> Pre-emptive ganciclovir IV 5 mg/kg every 12 hours for 7 days
Outcomes	<ol style="list-style-type: none"> CMV disease and syndrome All-cause mortality Other infections Adverse events Cost analysis
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: pp65 antigenaemia > 1 positive cell/20 x 10⁴

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However, different administration routes were used and considered not to be blinded. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	All outcomes specified in methods were reported; however, graft loss and acute rejection were not reported
Other bias	Unclear risk	No sponsorship of study was stated

Witzke 2012 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT
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Witzke 2012 Kidney (Continued)

- Follow-up period: 12 months

Participants	<ul style="list-style-type: none"> • Country: Germany/Austria • Setting: Multicentre • CMV status: D+/R+, D-/R+ • Kidney transplant recipients • Number: 296 • Mean age $\pm$ SD: treatment group (54.2 ± 12.0 years); control group (51.1 ± 13.6 years)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Pre-emptive oral valganciclovir 900 mg twice/d for at least 14 days or until test negative (< 400 copies/mL) with prophylaxis period consisting of 450 mg valganciclovir twice/d for 28 days <p>Control group</p> <ul style="list-style-type: none"> • Prophylactic oral valganciclovir 900 mg twice/d for 100 days initiated within 14 days post transplantation
Outcomes	<ol style="list-style-type: none"> 1. CMV disease and syndrome 2. CMV infection 3. Other infections 4. Adverse events 5. All-cause mortality 6. Acute rejection 7. Graft loss
Notes	<ul style="list-style-type: none"> • Method for CMV detection was RT-PCR with cut off value > 400 copies/mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified
Allocation concealment (selection bias)	Low risk	1:1 central allocation via phone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-labelled. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	All outcomes specified in methods are reported and all outcomes of importance were included
Other bias	High risk	Valganciclovir was supplied by Roche Pharma AG, Germany

Yang 1998 Kidney

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Follow-up period: 6 months
Participants	<ul style="list-style-type: none"> Country: South Korea Setting: University CMV status: D/R+ Kidney transplant recipients Number: 31 Mean age: NS
Interventions	Treatment group <ul style="list-style-type: none"> Pre-emptive IV ganciclovir 5 mg/kg twice/d for 2 weeks Control group <ul style="list-style-type: none"> No treatment
Outcomes	<ol style="list-style-type: none"> CMV syndrome and disease CMV infection
Notes	<ul style="list-style-type: none"> Method for detection of CMV infection: pp65 antigenaemia > 1 positive cell/5 x 10⁴; CMV IgM index > 0.500

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported but method not specified
Allocation concealment (selection bias)	Unclear risk	Authors did not report method used to conceal allocation of patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However, no placebo was given to the untreated control group. This would enable investigators to identify participant's groups. The interpretation of clinical symptoms could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome analysis was likely performed by the study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	High risk	All outcomes specified in methods were reported; however, death, graft loss and acute rejection outcomes were not reported
Other bias	Low risk	Study was supported by a research grant from the Clinical Research fund (BKB) of the Catholic Medical Centre

CMV - cytomegalovirus; DNA - deoxyribonucleic acid; D/R+ donor unknown/recipient CMV positive; D+/R- donor CMV positive/recipient CMV negative; D-/R- donor CMV negative/recipient CMV negative; IV - intravenous; NaCl - sodium chloride; NS - not stated; PCR - polymerase chain reaction; SD - standard deviation; SE - standard error

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahsan 1997 Kidney	Prophylaxis RCT
Ahsan 1998	Not RCT (sequential)
Arbo 2000	Economic evaluation of previous study
Badley 1997 Liver	Prophylaxis RCT
Balfour 1989 Kidney	Prophylaxis RCT
Barkholt 1999 Liver	Prophylaxis RCT
Brennan 1997b Kidney	Not a pre-emptive study and primary outcome was herpes virus (HHV-7) infection
Cohen 1993 Liver	Prophylaxis RCT
Conti 1995 Kidney	Prophylaxis RCT
Denny 2002	Not an RCT
Devolder 2010	Ineligible intervention
Dickinson 1996	IgG to prevent CMV
Duncan 1993 Lung	Prophylaxis RCT
Egan 2002 Heart	Prophylaxis RCT
Euro-SPK 2005	RCT comparing tacrolimus and cyclosporin
Falagas 1997	Included both non-randomised patients and patients from a previous study
Fehir 1989	Non-randomised patients included
Ferreira 2004	CMV data from several studies comparing immunosuppressive regimens
Fishman 2000	Retrospective study
Flechner 1998 Kidney	Prophylaxis RCT
Gane 1997 Liver	Prophylaxis RCT
Gavalda 1997 Liver	Prophylaxis RCT
Gerna 2003	Qualitative molecular assay for detection of a late (pp67) HCMV mRNA versus quantitative antigenaemia
Gerna 2007	Evaluation of cytomegalovirus DNAemia versus pp65-antigenaemia

Study	Reason for exclusion
Green 1997 Liver	Prophylaxis RCT
Greger 1988	Comparison of immunosuppression regimes
Griffiths 2010	Ineligible intervention (haematopoietic stem cell transplant recipients)
Hecht 1988	Case reports of patients treated with ganciclovir
Hertz 1998 Heart/Lung	Prophylaxis RCT
Hibberd 1995 Kidney	Prophylaxis RCT
IMPACT Study 2010 TX	Prophylaxis RCT
Jurim 1996	Subgroup of previous study; outcome hepatitis B
Kim 2000	Economic evaluation of previous study
King 1999	IgG versus antiviral to prevent CMV
Kletzmayer 1996 Kidney	Prophylaxis RCT
Kletzmayer 2000	Not RCT; historical controls
Leray 1995 Kidney	Prophylaxis RCT
Lowance 1999 Kidney	Prophylaxis RCT
Lumbreras 1993	Not RCT; historical controls
MacDonald 1991	Ineligible intervention
Macdonald 1995 Heart	Prophylaxis RCT
Marker 1980	Intervention study. Included both randomised and non-randomised participants
Mattes 2004	Included non-solid organ transplants in analysis
Merigan 1992 Heart	Prophylaxis RCT
Moreno 1999	Not RCT
Mullen 1998	Retrospective study
Murray 1997	Economic evaluation of CMV treatments
Nakazato 1993 Liver	Prophylaxis RCT
Palmer 2010	Prophylaxis RCT
Paya 2004 All	Prophylaxis RCT
Pescovitz 2009	Prophylaxis RCT
Pouteil 1991	HLA compatibility with CMV infection

Study	Reason for exclusion
Pouteil-Noble 1996 Kidney	Prophylaxis RCT
Qiu 2008 Kidney	Not an RCT
Reischig 2005 Kidney	Prophylaxis RCT
Rondeau 1993 Kidney	Prophylaxis RCT
Rostaing 1994 Kidney	Prophylaxis RCT
Rubin 2002 All	Prophylaxis RCT
Saliba 1993 Liver	Prophylaxis RCT
Schnitzler 2000	Re-analysis of previous study (1992)
Singh 1995	Not RCT
Singh 2002	Prophylaxis RCT
Speich 1999	Not RCT; sequential enrolment
Tian 2005 Kidney	Not RCT
Tong 2002	Primary outcome was herpes virus (HHV-7) infection
Turgeon 1998	Not RCT; sequential enrolment
Valantine 1999	Post hoc analysis
VICTOR Study 2007	Treatment study. Assessed genetic polymorphism impact on CMV infection and other herpes virus co-infections
Villano 2010	Prophylaxis RCT
Winston 1995 Liver	Prophylaxis RCT
Winston 2003 Liver	Prophylaxis RCT
Winston 2004 Liver	Prophylaxis RCT
Yang 1999	Unable to determine if participants were randomised

CMV - cytomegalovirus; RCT - randomised control trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Scott 2011 Liver

Methods	Open label RCT, sequentially numbered envelopes.
Participants	<ol style="list-style-type: none"> 1. Male or female > 16 years of age 2. Patients undergoing liver transplantation 3. Single or multi-organ transplant 4. Patients meet transplant criteria

Scott 2011 Liver (Continued)

	5. Chronic liver disease or fulminant hepatic failure 6. Able to give written informed consent
Interventions	<p>High risk group and prophylaxis group are assigned to receive 900mg (two 450mg tablets) of valganciclovir (Valcyte) once daily for 3 months commenced within 72 hrs after liver transplantation and monitored regularly for CMV infection/disease. Dose will be changed based on creatinine clearance.</p> <p>Pre-Emptive group Monitored regularly for CMV infection only. If this occurs patients will be given 5 mg/kg intravenously over one hour, of ganciclovir (GCV) twice daily for 2 weeks CMV infection is determined on testing with Qualitative Polymerase chain reaction (PCR)</p> <p>Valganciclovir doses as per creatinine clearance: Creatinine clearance ≥ 60 ml/min 900mg daily Creatinine clearance 40-59 ml/min 450mg daily Creatinine clearance 25-39 ml/min 450mg second daily Creatinine clearance 10-24 ml/min 450 mg twice weekly</p>
Outcomes	Primary incidence of CMV infection and disease Assess viral characteristics of infection Antiviral resistant CMV Incidence of opportunistic viral infections Drug efficacy
Notes	Unfunded

Characteristics of ongoing studies [ordered by study ID]

NCT00372229

Trial name or title	A randomized trial comparing valcyte CMV prophylaxis versus pre-emptive therapy after renal transplantation using proteomics for monitoring of graft alteration
Methods	Open label RCT
Participants	Unknown
Interventions	Valganciclovir CMV prophylaxis for 100 days versus valganciclovir pre-emptive therapy
Outcomes	CMV infection CMV disease Graft loss
Starting date	May 2006
Contact information	
Notes	

NCT00966836

Trial name or title	Prevention of transplant atherosclerosis with everolimus and anti-cytomegalovirus therapy
Methods	Open label RCT
Participants	Estimated 100
Interventions	Pre-emptive strategy with valganciclovir plus everolimus Prophylaxis with valganciclovir plus mycophenolate Prophylaxis with valganciclovir plus everolimus Pre-emptive mycophenolate
Outcomes	CMV infection
Starting date	April 2009
Contact information	Luciano Potena, MD PhD Francesco Grigioni, MD PhD
Notes	

NCT01552369

Trial name or title	Prophylaxis versus preemptive therapy for the prevention of CMV in high-risk R-D+ liver transplant recipients
Methods	Single blind (outcome assessors), RCT
Participants	Estimated 180
Interventions	Prophylaxis with valganciclovir for 100 days post transplantation versus subjects monitored with CMV PCR testing and given valganciclovir therapy only if PCR is positive. Therapy is stopped after second negative PCR test
Outcomes	CMV disease All-cause mortality
Starting date	July 2012
Contact information	Principal Investigator: Nina Singh, MD
Notes	

DATA AND ANALYSES

Comparison 1. Pre-emptive medication for CMV viraemia versus placebo or standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All symptomatic CMV disease	6	288	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.11, 0.80]
2 CMV organ involvement	5	217	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.63]
3 CMV associated symptoms	5	217	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.21]
4 Acute rejection	3	185	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.69, 2.12]
5 All-cause mortality and graft loss	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 All-cause mortality	3	176	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.35, 4.30]
5.2 Graft loss	1	36	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 5.35]
6 Other infections	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Leucopenia	2	114	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.16, 15.36]
7.2 Kidney dysfunction	1	36	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.18, 4.92]

Analysis 1.1. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 1 All symptomatic CMV disease.

Analysis 1.2. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 2 CMV organ involvement.

Analysis 1.3. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 3 CMV associated symptoms.

Analysis 1.4. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 4 Acute rejection.

Analysis 1.5. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 5 All-cause mortality and graft loss.

Analysis 1.6. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 6 Other infections.

Analysis 1.7. Comparison 1 Pre-emptive medication for CMV viraemia versus placebo or standard care, Outcome 7 Adverse effects.

Comparison 2. Pre-emptive medication versus prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All symptomatic CMV disease	7	753	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.43, 2.44]
2 CMV infection	7	727	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.44, 2.96]
3 All-cause mortality and graft loss	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All-cause mortality	7	753	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.56, 2.51]
3.2 Graft loss	7	753	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.41, 2.82]
4 Acute rejection	6	693	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.75, 2.03]
5 Other infections	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Bacterial	2	168	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.43]
5.2 Viral	1	70	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.92, 2.70]
5.3 Fungal	1	70	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.18, 19.89]
6 Adverse effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Leucopenia	6	729	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.20, 0.90]
6.2 Neurological dysfunction	3	187	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.17, 1.96]
6.3 Kidney dysfunction	1	47	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.11]
6.4 Anaemia	2	218	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.48, 1.73]
6.5 Thrombocytopenia	2	218	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.54, 2.48]
6.6 Malignancy	1	70	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.48]
6.7 Hypertension	1	70	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.27]
6.8 Hypercholesterolaemia	1	70	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.10]
6.9 Cardiac events	1	70	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.10 Neutropenia	3	514	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.27, 0.95]
7 D+/R- serostatus	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Symptomatic CMV	2	39	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.12, 8.02]
7.2 CMV infection	2	39	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.71, 1.92]
8 D+ or D-/R+ serostatus	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Symptomatic CMV	2	129	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.02, 1.74]
8.2 CMV infection	2	129	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.25, 3.42]

Analysis 2.1. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 1 All symptomatic CMV disease.

Analysis 2.2. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 2 CMV infection.

Study or subgroup	Pre-emptive n/N	Prophylaxis n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 208 (Pre-emptive), 84 (Prophylaxis)					
Heterogeneity: $\tau^2=0.15$; $\chi^2=20.78$, $df=6$ ($P=0$); $I^2=71.13\%$					
Test for overall effect: $Z=3.91$ ($P<0.0001$)					
			Pre-emptive 0.002 0.1 1 10 500 Prophylaxis		

Analysis 2.3. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 3 All-cause mortality and graft loss.

Study or subgroup	Pre-emptive n/N	Prophylaxis n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 All-cause mortality					
Khoury 2006 Kidney	0/49	0/49			Not estimable
Reischig 2008 Kidney	0/36	1/34		5.62%	0.32[0.01,7.48]
Queiroga 2003 Kidney	5/25	0/9		7.18%	4.23[0.26,69.69]
Jung 2001 Kidney	4/36	1/34		12.29%	3.78[0.44,32.13]
Witzke 2012 Kidney	2/150	2/146		14.86%	0.97[0.14,6.82]
Singh 1994 Liver	3/23	3/24		25.22%	1.04[0.23,4.65]
Kliem 2008 Kidney	4/65	5/73		34.84%	0.9[0.25,3.2]
Subtotal (95% CI)	384	369		100%	1.19[0.56,2.51]
Total events: 18 (Pre-emptive), 12 (Prophylaxis)					
Heterogeneity: $\tau^2=0$; $\chi^2=2.89$, $df=5$ ($P=0.72$); $I^2=0\%$					
Test for overall effect: $Z=0.45$ ($P=0.65$)					
2.3.2 Graft loss					
Khoury 2006 Kidney	1/49	0/49		7.46%	3[0.13,71.89]
Jung 2001 Kidney	0/36	4/34		8.68%	0.11[0.01,1.88]
Singh 1994 Liver	4/23	0/24		8.77%	9.38[0.53,164.94]
Reischig 2008 Kidney	1/36	3/34		12.7%	0.31[0.03,2.88]
Queiroga 2003 Kidney	3/25	1/9		13.36%	1.08[0.13,9.1]
Witzke 2012 Kidney	4/150	7/146		23.79%	0.56[0.17,1.86]
Kliem 2008 Kidney	10/65	4/73		25.23%	2.81[0.93,8.52]
Subtotal (95% CI)	384	369		100%	1.07[0.41,2.82]
Total events: 23 (Pre-emptive), 19 (Prophylaxis)					
Heterogeneity: $\tau^2=0.65$; $\chi^2=10.25$, $df=6$ ($P=0.11$); $I^2=41.45\%$					
Test for overall effect: $Z=0.14$ ($P=0.89$)					
			Pre-emptive 0.005 0.1 1 10 200 Prophylaxis		

Analysis 2.4. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 4 Acute rejection.

Study or subgroup	Pre-emptive n/N	Prophylaxis n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gerna 2008 Liver	2/11	1/10		4.39%	1.82[0.19,17.12]
Jung 2001 Kidney	4/49	1/49		4.71%	4[0.46,34.52]
Reischig 2008 Kidney	13/36	5/34		17.25%	2.46[0.98,6.15]
Khoury 2006 Kidney	9/36	9/34		20.23%	0.94[0.43,2.09]
Kliem 2008 Kidney	18/65	14/73		25.66%	1.44[0.78,2.67]
Witzke 2012 Kidney	18/150	27/146		27.75%	0.65[0.37,1.13]
			Pre-emptive 0.01 0.1 1 10 100 Prophylaxis

Analysis 2.5. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 5 Other infections.

Analysis 2.6. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 6 Adverse effects.

Analysis 2.7. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 7 D+/R- serostatus.

Analysis 2.8. Comparison 2 Pre-emptive medication versus prophylaxis, Outcome 8 D+ or D-/R+ serostatus.

Comparison 3. Oral versus IV ganciclovir

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All symptomatic CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Other infections	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Oral versus IV ganciclovir, Outcome 1 All symptomatic CMV disease.

Analysis 3.2. Comparison 3 Oral versus IV ganciclovir, Outcome 2 All-cause mortality.

Analysis 3.3. Comparison 3 Oral versus IV ganciclovir, Outcome 3 Other infections.

Study or subgroup	Oral ganciclovir		IV ganciclovir		Risk Ratio		Risk Ratio	
	n/N		n/N		M-H, Random, 95% CI		M-H, Random, 95% CI	
Singh 2000 Liver	5/11		5/11				1[0.4,2.5]	
					Oral ganciclovir 0.2 0.5 1 2 5		IV ganciclovir	

ADDITIONAL TABLES

Table 1. Summary of CMV guidelines for solid organ transplant recipients

	The Kidney Disease Improving Global Outcomes (KDIGO 2009)	Caring for Australians with Renal Impairment (CARI 2010)	British Transplant Society (BTS 2011)
Current recommendations to prevent CMV disease	Valganciclovir or IV ganciclovir prophylaxis for at least 3 months post renal transplantation and for 6 weeks post T-cell depleting immunosuppression. No prophylaxis is required for renal transplant patients who are CMV seronegative and receive a seronegative transplant	Valganciclovir, valaciclovir or IV ganciclovir for prophylaxis for 3 months. This is extended to 6 months for high risk patients (D+/R-). No prophylaxis is required for transplant recipients who are CMV seronegative and receive a seronegative transplant	Valganciclovir or IV ganciclovir for prophylaxis 100 days post transplantation. No prophylaxis is required for renal or liver transplant patients who are seropositive for CMV and do not receive T-cell depleting immunosuppression

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor Cytomegalovirus, this term only in MeSH products 2. MeSH descriptor Cytomegalovirus Infections explode all trees in MeSH products 3. MeSH descriptor Cytomegalovirus Vaccines explode all trees 4. cytomegalovirus* in All Fields in CENTRAL 5. cmv* in All Fields in CENTRAL 6. (#1 OR #2 OR #3 OR #4 OR #5) 7. (organ or renal or kidney or heart or lung or liver or pancreas) adj transplant in All Fields in all products 8. MeSH descriptor Organ Transplantation, this term only 9. MeSH descriptor Heart Transplantation explode all trees 10. MeSH descriptor Lung Transplantation explode all trees 11. MeSH descriptor Kidney Transplantation, this term only 12. MeSH descriptor Liver Transplantation, this term only 13. MeSH descriptor Pancreas Transplantation, this term only 14. (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) 15. (#6 AND #14)

(Continued)

MEDLINE (OVID SP)	<ol style="list-style-type: none"> 1. Cytomegalovirus/ 2. exp Cytomegalovirus Infections/ 3. Cytomegalovirus Vaccines/ 4. cytomegalovirus.tw. 5. cmv.tw. 6. or/1-5 7. Organ Transplantation/ 8. exp Heart Transplantation/ 9. exp Lung Transplantation/ 10. Kidney Transplantation/ 11. Liver Transplantation/ 12. Pancreas Transplantation 13. ((organ or renal or kidney or heart or lung or liver or pancreas) adj transplant\$.tw 14. or/6-12 15. and/6,15
EMBASE (OVID SP)	<ol style="list-style-type: none"> 1. exp CYTOMEGALOVIRUS/ 2. Cytomegalovirus Infection/ 3. Cytomegalovirus Antibody/ 4. Cytomegalovirus Vaccine/ 5. cytomegalovirus.tw. 6. CMV.tw. 7. or/1-6 8. exp organ transplantation/ 9. ((organ or renal or kidney or heart or lung or liver or pancreas) adj transplant\$.tw. 10. or/8-9 11. 7 and 10

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or</p>

(Continued)

	non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	<i>Unclear:</i> Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.</p> <p><i>High risk of bias:</i> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Selective reporting Reporting bias due to selective outcome reporting	<p><i>Low risk of bias:</i> The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).</p> <p><i>High risk of bias:</i> Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.</p>

(Continued)

Unclear: Insufficient information to permit judgement

Other bias

Low risk of bias: The study appears to be free of other sources of bias.

Bias due to problems not covered elsewhere in the table

High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
16 January 2013	New search has been performed	Five studies identified and included
16 January 2013	New citation required and conclusions have changed	New outcome data available

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 1, 2006

Date	Event	Description
19 January 2010	Amended	Contact details updated.
13 August 2009	Amended	Contact details updated.
14 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

2013 review update

- DO, AW, GS, KK and EH contributed to the data extraction, quality assessment, data analysis and rewriting of the review update.

2005 review

- EMH identified and extracted data from included studies, contacted authors, analysed and interpreted the results and wrote the manuscript.
- CAJ conceived, designed and developed the protocol and search strategy for the review, identified and extracted data from included studies and participated in revision of the manuscript.
- GFMS checked the analysis and interpretation of the results and participated in the revision of the manuscript.
- KK identified and extracted data from included studies and participated in revision of the manuscript.
- JCC conceived, designed and developed the protocol, analysed and interpreted the results and edited the drafting and revision of the manuscript.

DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Organ Transplantation; Acyclovir [therapeutic use]; Antiviral Agents [*therapeutic use]; Cytomegalovirus Infections [*prevention & control]; Ganciclovir [therapeutic use]; Immunocompromised Host; Opportunistic Infections [prevention & control]; Randomized Controlled Trials as Topic; Viremia [*prevention & control] [virology]

MeSH check words

Humans