Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation


Authors' objectives
To develop a set of comprehensive, standardised evidence-based guidelines for the use of antiviral therapy to prevent cytomegalovirus (CMV) disease in adult patients having undergone renal transplantation.

Searching
MEDLINE was searched from 1976 to July 1997 using the following terms: antiviral agents, ganciclovir, acyclovir, immunoglobulin (therapeutic use), kidney transplant, organ transplant, heart transplant, liver transplant, cytomegalovirus (CMV) infection, herpesviridae infection, prevalence, and incidence. Additional information was obtained from pharmaceutical companies responsible for the distribution of anti-CMV therapies, handsearches of the two most recent American Congress of Nephrology meetings and the American Society of Transplant Physicians Abstracts (CD-ROM 1996), review articles and from experts in the field.

Study selection
Study designs of evaluations included in the review
Studies that evaluated antiviral therapy in prevention of CMV virus after organ transplant were included. Randomised controlled trials (RCTs), non-randomised controlled trials, observational studies and cohort studies were reported.

Specific interventions included in the review
The following drug therapies were included: passive immunisation with human immunoglobulin including non-specific globulin and CMV-specific hyperimmune globulin; acyclovir; and ganciclovir. These drugs were either used alone or in combination and were compared with each other or with placebo or no therapy.

Participants included in the review
The main focus was on patients who had undergone renal transplant, though patients who had undergone other organ transplants (solid organ, heart or liver) were also included.

Outcomes assessed in the review
The control of symptoms and features of CMV disease over the first 6 months to 1 year after transplantation was assessed. Only serious clinical disease requiring hospitalisation was considered.

How were decisions on the relevance of primary studies made?
Identified articles were reviewed by representatives of nephrology, microbiology, pharmacy, and epidemiology.

Assessment of study quality
Validity was assessed using the following criteria: use of blinded randomisation; use of placebo or control limb; blinded outcome assessment using well-defined criteria; the exclusion or loss to follow-up of less than 20% of randomised patients; no co-intervention with drugs or unclear descriptions of immunosuppressive regimes; and appropriate statistical testing. In the absence of blinding, outcome assessment by adjudication was accepted. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Details of methods used to extract data and type of data extracted were not reported. From the tables it appears that the following data were extracted: author, date of publication; intervention details; population details; randomised or not;
outcomes blinding; co-interventions; and results. Results of individual studies were reported as relative risk (RR) of disease and number needed to treat (NNT) usually with 95% confidence intervals. Estimates of risk or benefit were calculated using best and worst case scenarios for some studies.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
Studies were grouped by patient and donor serological group and by intervention regimes. Recommendations were based on the strength of the evidence using categories A through E. Grade A recommendations (for the intervention) and grade E (against the intervention) were supported by high quality studies, usually type 1 RCT. Grade B and D recommendations were given when evidence was less convincing, usually for cohort or other non randomised controlled studies. Grade C indicates there is insufficient or contradictory evidence either against or for the intervention.

**Results of the review**

Twenty-six studies were presented in a table, including 21 randomised studies (7 of which were blinded) and 14 observational studies. The exact number included was unclear.

1. Seropositive recipient; donor seropositive or seronegative; immunosuppression with antilymphocytic products 3 RCTs in renal transplant patients): benefit was reported for both ganciclovir and acyclovir. 2 good quality RCTs (171 patients) compared ganciclovir with no therapy and reported RR = 0.27 (95% CI: 0.12, 0.64) and RR = 0.84 (95% CI: 0.04, 0.65). Side effect was reported in 1/40 patient in one RCT. One low quality RCT reported benefit in patients treated with high doses of acyclovir (no further details were presented): RR = 0.26 (95% CI: 0.09, 0.75). 5 RCTs in other solid organ transplants supported this.

2. Seronegative recipient; donor seropositive; immunosuppression with antilymphocytic products (2 RCTs in renal transplant patients): Significant benefit was reported for oral acyclovir and a positive but non-significant trend for ganciclovir. One small RCT (32 patients) found no significant difference between ganciclovir compared to no therapy with RR = 0.64 (95% CI: 0.36, 1.16). One RCT (number of patients not reported) found significant benefit for oral acyclovir compared to placebo with RR = 0.26 (95% CI: 0.09, 0.75). No comparison studies were identified.

Other evidence was considered from extrapolation from 2 studies in responder for CMV positive and donor negative for CMV + and D +/- renal transplant patients and RCTs in heart and liver transplant patients.

3. Seronegative recipient; donor seropositive; conventional immunosuppression: (1 RCT, 99 renal transplant patients): High exclusion rate post randomisation makes conclusions indeterminate (40 out of 99 patient excluded). Study reported a significant reduction in CMV associated syndromes in patients treated with passive immunisation compared to no-treatment with RR = 0.35. Using a worst case and best case scenario in an intention-to-treat analysis gave RR ranges from 1.75 to 0.10 and NNT ranges from -4 to 1.8.

Risk of disease was estimated at 10% to 40% across 7 trials.

4. Seronegative recipient; donor seronegative; any immunosuppressive regime: No trials of treatment were identified. Low prevalence of disease was reported in 9 observational or cohort studies.

5. Seropositive recipient; donor seropositive or seronegative; conventional immunosuppression: few studies have examined the effect of different regimes.

Sub-group analysis from 1 RCT in renal transplant patients (number of patients not reported) suggested benefit for acyclovir over placebo but the strength of evidence was insufficient to make any recommendation.
Cost information
Higher mean total institutional costs were reported for patients with CMV than for control subjects ($42,611 vs $17,309 in 1997 Canadian dollars; P = 0.001).

The cost of administering therapy to a CMV seronegative recipient of a seronegative donor was estimated at $1.68 million (US) per life saved compared with costs of $29,800 (US) for a seronegative recipient of a seropositive donor.

Current cost of a 2-week course of intravenous ganciclovir is >$1966.12 (CAN). Assuming that hospital costs for one case of CMV average $25,302 (CAN), cost-equivalency would be achieved if 12.9 patients were given prophylaxis for each case of CMV prevented.

Authors’ conclusions
The authors report the following clinical recommendations:

1. Seropositive recipient; donor seropositive or seronegative; immunosuppression with antilymphocytic products. Prophylaxis with antiviral therapy recommended (grade A recommendation). Drug of choice is unknown but prophylaxis with oral or intravenous ganciclovir for a minimum period of 14 days is recommended.

2. Seronegative recipient; donor seropositive; immunosuppression with antilymphocytic products. Prophylaxis with antiviral therapy recommended (grade A recommendation). Ganciclovir for a minimum period of 14 days is recommended.

3. Seronegative recipient; donor seropositive; conventional immunosuppression. Prophylaxis with antiviral therapy recommended (grade B recommendation).

4. Seronegative recipient; donor seronegative; any immunosuppressive regime. No prophylaxis with antiviral therapy required (grade D/E recommendation).

5. Seropositive recipient; donor seropositive or seronegative; conventional immunosuppression. Prophylaxis left to discrimination of physician in charge (grade C recommendation).

CRD commentary
The aims were stated. The search strategy explored several potential sources of relevant studies including unpublished studies. Validity was assessed using pre-defined criteria and comment made on validity both in the table of study details and in the text. Details of some of the included studies were presented in tabular format although it was not clear exactly how many studies were included. Costs were reported.

Inclusion criteria for studies were not defined. Methods used for study selection, validity assessment and data extraction were not reported. Adverse reactions were only mentioned briefly.

The authors' conclusions were supported by the evidence although caution is required because it is not clear how many studies were included.

Implications of the review for practice and research
Practice: The authors' clinical recommendations were as follows.

1. Seropositive recipient; donor seropositive or seronegative; immunosuppression with antilymphocytic products. Prophylaxis with antiviral therapy recommended (grade A recommendation). Drug of choice is unknown but prophylaxis with oral or intravenous ganciclovir for a minimum period of 14 days is recommended.

2. Seronegative recipient; donor seropositive; immunosuppression with antilymphocytic products. Prophylaxis with antiviral therapy recommended (grade A recommendation). Ganciclovir for a minimum period of 14 days is recommended.
3. Seronegative recipient; donor seropositive; conventional immunosuppression. Prophylaxis with antiviral therapy recommended (grade B recommendation).

4. Seronegative recipient; donor seronegative; any immunosuppressive regime. No prophylaxis with antiviral therapy required (grade D/E recommendation).

5. Seropositive recipient; donor seropositive or seronegative; conventional immunosuppression. Prophylaxis left to discrimination of physician in charge (grade C recommendation).

Research: The authors state that further research is required into the treatment of CMV after renal transplantation. Clarification is required of definitions used and diagnostic criteria. Unresolved issues include the optimal duration of prophylactic therapy and the use of combination protocols.

Bibliographic details

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.