Clinical Practice Guidelines: Prevention of Cytomegalovirus Disease After Renal Transplantation

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Abstract. Objective: To develop a set of comprehensive, standardized, evidence-based guidelines for the use of antiviral therapy to prevent cytomegalovirus disease in adult patients having undergone renal transplantation. Options: The use of medication, at the time of induction therapy, or at the earliest sign of viremia. Treatments were evaluated by patient and donor serologic groups and the induction regimen used. Outcomes: The control of symptoms and features of cytomegalovirus disease over the first 6 mo to 1 yr after transplantation. Evidence: Articles, compiled using a MEDLINE search from 1976 to July 1997, were reviewed by representatives of nephrology, microbiology, pharmacy, and epidemiology. Additional information was obtained from recent review articles and conference abstracts, and from experts in the field. Values: The evidence-based methods and values of the Canadian Task Force on the Periodic Health Examinations were used. High value was placed on studies with a randomized controlled design and blinded outcome observers. Study quality was classified as poor when cointervention was present (especially with regard to immunosuppressive regimens), when more than 20% of patients were lost to follow-up, and when intention to treat analysis was not performed. Recommendations were made with a graded system (grades A and B: Use of the intervention advised, based on high or fair quality evidence, respectively; grades D and E: Use of the intervention not advised, based on high or fair quality evidence, respectively; grade C: No recommendation made because of insufficient or conflicting evidence). Recommendations: (1) Seropositive recipient; donor seropositive or seronegative; immunosuppression with antilymphocyte products. Prophylaxis with antiviral therapy recommended (grade A recommendation). (2) Seronegative recipient; seropositive donor; immunosuppression with antilymphocyte products. Prophylaxis with antiviral therapy recommended (grade A recommendation) (3) Seronegative recipient; seropositive donor; conventional immunosuppression. Prophylaxis with antiviral therapy recommended (grade A recommendation). (4) Seronegative recipient; seropositive donor; any immunosuppressive regimen. No prophylaxis with antiviral therapy required (grade D/E recommendation). (5) Seropositive recipient; donor seropositive or seronegative; conventional immunosuppression. Prophylaxis left to the discrimination of the physician in charge (grade C recommendation).

This article presents practical guidelines for clinicians caring for renal transplant patients in the immediate posttransplant period. The goal is to help clinicians define treatment protocols based on the evidence available and on the recommendations of the Evidence-Based Working Group and the National Health Institute guidelines (1,2). It differs from previous literature reviews in that strict evidence-based approaches were used and scientific rigor was applied in the evaluation of the literature. All recommendations were made, by consensus, based on the evidence available. Newer methodologies and treatments, which remain unproven, are discussed briefly as future directions.

Materials and Methods

Evidence is presented using the principles adopted by the Canadian Task Force on the Periodic Health Examination (3). The recommendations, depending on the strength of the evidence, are graded using categories A through E. The strongest recommendations (grade A, in support of the preventative intervention, or grade E, against the use of the intervention) are given only if the intervention is supported by or negated by high quality studies, usually type I randomized controlled studies. Grade B and D recommendations are given when there is less convincing evidence, usually from cohort or other nonrandomized controlled studies (type II evidence). Data from randomized controlled studies believed to be susceptible to bias or methodologic concerns were given the same weight as type II studies. Grade C
recommendations indicate that there is insufficient or contradictory evidence either against or for the intervention in question. In this situation, the physician or decision maker should base their treatment on individualized clinical criteria.

Publications and articles for this review were identified using a MEDLINE search for the period 1976 to July 1997. The following search terms were used: antiviral agents, ganciclovir, acyclovir, immunoglobulin (therapeutic use), kidney transplant, organ transplant, heart transplant, liver transplant, cytomegalovirus (CMV) infection, herpesviridae infection, prevalence, and incidence. Articles were limited to studies in humans. Additional data references were obtained from the pharmaceutical companies responsible for the distribution of anti-CMV therapies and from hand searches of the abstracts from the two most recent American Society of Nephrology meetings and the American Society of Transplant Physicians Abstracts (CD-ROM 1996). To ensure validity of the data, each of the studies reviewed was checked against six criteria. These criteria included blinded randomization, the use of a placebo or control arm, blinded outcome assessment using well defined criteria, the exclusion or loss to follow-up of less than 20% of randomized patients, no cointervention with other drugs (or unclear descriptions of immunosuppression regimens), and appropriate statistical testing. In the absence of blinding, outcome assessment by an adjudication committee was accepted. The only outcomes chosen were those considered as serious clinical disease requiring hospitalization.

Results are reported as the relative risk (RR) of disease, the relative risk reduction (RRR) with therapy, and the number needed to treat (NNT) to prevent one case of disease (4,5). Most results included 95% confidence intervals (95% CI), and some included estimates of risk (or benefit) after reconsideration of the data using worst case and best case scenarios. All epidemiologic principles were derived from the principles taught by the Evidence-Based Working Group and the Canadian Task Force for Periodic Health (6,7).

To ensure unbiased representation, all clinicians involved with renal transplantation within the University of Toronto campus were invited to participate. In addition, representation was actively sought from those in general nephrology, clinical epidemiology, pharmacy, and infectious disease specialties. Only one invited clinician chose to not participate.

Background Information

CMV is prevalent in most communities. The virus is characterized by its ability to remain latent in the body and to cause active disease during periods of immune stress or immunosuppression. Exposure to the virus often results in the production of a lifelong CMV-specific antibody (seroconversion). In transplant recipients, the prevalence of clinical disease is related to the organ transplanted (being highest in bone marrow transplant recipients and lowest in renal patients), to donor and recipient serology pretransplantation, and to the type and dose of immunosuppression given (8,9). Active viral infection, defined by the presence of viral particles in the blood, does not always cause symptoms of disease and hence the spectrum of CMV disease is wide.

The Burden of Suffering

The burden of suffering can be considered either as the cost to medical resources or the impact on the patient. In terms of hospital care, a retrospective case-control study has shown prolonged hospitalization (from a mean hospital stay of 22 to 59 d) and a 2.5-fold increase in institutional costs in patients with CMV disease (10).

Patient impact may be measured as the reported prevalence of symptomatic disease in the literature. A number of observational studies were examined, but each differed in the study population reviewed, the methodology used to detect disease, and the definitions used. A brief summary is given in Table 1. The most recent series report that 8 to 11% of all renal transplant recipients had CMV syndrome and that an additional 7% had manifestations of serious invasive disease. If accurate, this represents a significant component of health care expenditure (11,12).

Recent reports suggest a fourfold increase in graft loss at 3 yr in association with seropositive CMV donor status (13). The association is demonstrated in data from the U.S. Renal Data System database and is supported by other study observations, but to date no study has confirmed causation (14–17). Because increased immunosuppression for the treatment of acute rejection may lead to an increased incidence of CMV disease, cause and effect cannot be easily differentiated. The data do suggest a higher rate of graft loss in patients transplanted with a kidney from a seropositive donor but do not demonstrate a higher rate of graft loss in recipient-positive/donor-negative transplant recipients. If true, an association between CMV disease and increased graft loss would change the clinical significance of these recommendations.

Possible Interventions

Three different drug therapies were considered. These included passive immunization with human immunoglobulin, acyclovir, and ganciclovir. All pharmacologic interventions were considered collectively for the purposes of the recommendations. A summary of the evidence supporting each pharmacologic intervention is covered. However, an in-depth review of each intervention was deemed to be beyond the scope of this article. A summary of most studies reviewed is given in Table 2.

Passive Immunization

Passive immunization, in the form of human immunoglobulin, is available in two preparations: nonspecific globulin, derived from many healthy volunteer blood donors, and a CMV-specific hyperimmune globulin (HCMVig), in which globulin from selected donors with high CMV antibody titers is pooled to produce a single plasma pool with a CMV antibody titer greater than 1 in 7000. Both preparations are administered intravenously at set intervals, usually over the first 10 to 16 wk posttransplantation. Complications appear to be limited to fever, flushing, and nausea, and can be reduced by premedication with diphenhydramine, meperidine (pethidine), or steroids, as well as using slow infusion rates (18,19). Expert opinion remains divided on whether there are significant differences with HCMVig or nonspecific globulin therapy.

Although many observational or case-control studies have been published (14,19–26), the only blinded randomized controlled trial, in seronegative renal patients at risk of primary disease, compared the efficacy of hyperimmune globulin
Table 1. Studies showing effect of pretransplant serology on clinical CMV disease

<table>
<thead>
<tr>
<th>Study</th>
<th>±ALG</th>
<th>R-/D-</th>
<th>R-/D+</th>
<th>R+/D-</th>
<th>R+/D+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricontinental study 1996 (12)</td>
<td>Some</td>
<td>8%</td>
<td></td>
<td>tissue invasive disease overall</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.7%</td>
<td></td>
<td>CMV syndrome overall</td>
<td></td>
</tr>
<tr>
<td>Weir 1987 (11)</td>
<td>No</td>
<td>3 of 142</td>
<td>11 of 20</td>
<td>3 of 142 (includes R-/D- group)</td>
<td></td>
</tr>
<tr>
<td>Weir 1988 (74)</td>
<td>Some</td>
<td>0 of 36</td>
<td>6 of 33</td>
<td>1 of 72</td>
<td></td>
</tr>
<tr>
<td>Mancilla 1992 (75)</td>
<td>Some</td>
<td></td>
<td></td>
<td>9 of 123</td>
<td></td>
</tr>
<tr>
<td>Hibberd 1992 (76)</td>
<td>Yes</td>
<td>0 of 37</td>
<td>7 of 12</td>
<td>16 of 45</td>
<td></td>
</tr>
<tr>
<td>Peterson 1997 (77)</td>
<td>No</td>
<td>0 of 5</td>
<td>4 of 12</td>
<td>4 of 16</td>
<td>12 of 45</td>
</tr>
<tr>
<td>Metselaar 1989 (17)</td>
<td>No</td>
<td>0 of 7</td>
<td>6 of 12</td>
<td>9 of 54</td>
<td></td>
</tr>
<tr>
<td>Rubin 1977 (73)</td>
<td>?</td>
<td></td>
<td></td>
<td>26 of 68</td>
<td></td>
</tr>
<tr>
<td>Grundy 1988 (78)c</td>
<td>No</td>
<td>-</td>
<td>10 of 14</td>
<td>0 of 15</td>
<td>10 of 26</td>
</tr>
<tr>
<td>Metselaar 1989 (25)</td>
<td>Yes</td>
<td>0 of 8</td>
<td>7 of 9</td>
<td>6 of 23</td>
<td></td>
</tr>
<tr>
<td>Chatterjee 1986 (79)</td>
<td>No</td>
<td></td>
<td></td>
<td>12 of 33</td>
<td></td>
</tr>
<tr>
<td>Ho 1975 (80)</td>
<td>No</td>
<td>3 of 10</td>
<td>10 of 12</td>
<td>8 of 10</td>
<td></td>
</tr>
<tr>
<td>Cuhadaroglu 1992 (81)</td>
<td>No</td>
<td>4 of 12</td>
<td>5 of 18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conlon 1992 (82)</td>
<td>No</td>
<td>0 of 9</td>
<td>6 of 7</td>
<td>1 of 5</td>
<td>2 of 4</td>
</tr>
</tbody>
</table>

a CMV, cytomegalovirus; ALG, antilymphocyte globulin.
b Cointervention with acyclovir and ALG in some patients.
c Not all data given in article.

against no therapy (19). Although well designed, interpretation of the study results is limited by the high number of patients initially randomized but subsequently excluded from the analysis. The study reported a significant reduction in CMV-associated syndromes (from 60 to 21%) in patients treated with CMV immune globulin, with similar results in subgroup analyses. Using strict epidemiologic principles, reanalysis of the data on the 59 patients followed to study completion showed that the effective RRR remains significant but falls to 0.27 (95% CI, 0.09 to 0.86; NNT, 3.0 patients). Similarly, if one uses an intention to treat analysis and recalculates the risk reduction and NNT using a worst case and best case scenario, the RR ranges from 1.75 (suggesting harm from HCMVlg) to 0.10; (NNT, -4 to 1.8). In addition, the results are confounded by a higher frequency of use of antilymphocyte products in the control group compared with the treatment group (5 of 24 versus 12 of 35).

Subsequent open label studies and meta-analyses (27,28) indicate that HCMVlg may confer significant benefit against CMV disease (level II evidence); however, all have significant study design flaws or do not feature renal patients as the main study population. Supportive evidence, not specific to renal transplant patients, of a trend to benefit is available from a subsequent study in liver transplant patients. In this series, 141 of 146 patients randomized were followed for 1 yr. Rates of CMV disease fell from 31 to 19% (RR, 0.56; 95% CI, 0.28 to 1.18; not statistically significant) (29).

Acyclovir

Acyclovir is a potent inhibitor of viral DNA polymerase activity and has been shown to be efficacious in the management of infections caused by herpes viruses. However, its role in the management of CMV disease has been called into doubt because the active drug must first be phosphorylated into an active compound, a process dependent on the presence of thymidine kinase within the virus (30–32). Human CMV lacks this virus-specific kinase, rendering the CMV virus resistant to acyclovir in vitro. Cole and Balfour have shown that the relative mean inhibitory concentration required for an effective therapeutic effect is higher than that achieved by either oral or intravenous administration of acyclovir (33). Nevertheless, some (34–37), but not all (21,38–45), in vivo studies have shown a benefit in patients treated with high doses of oral or intravenous acyclovir. Balfour et al. demonstrated that regard-
Table 2. Evidence supporting efficacy of antiviral prophylaxis in transplant patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Population</th>
<th>Randomized?</th>
<th>Blinded Outcome</th>
<th>Cointervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hibberd 1995</td>
<td>Gan versus no Rx</td>
<td>Renal, R+ serology only, ALG, n = 131</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
<td>RR 0.27 (95% CI, 0.12 to 0.64)</td>
<td>Level 1 evidence</td>
</tr>
<tr>
<td>Conti 1995</td>
<td>Gan versus no Rx</td>
<td>Renal, R+ serology only, ALG, n = 40</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>RR 0.84 (95% CI, 0.04 to 0.65)</td>
<td>Level 1 evidence; SE reported in one patient</td>
</tr>
<tr>
<td>Rondeau 1993</td>
<td>Gan versus no Rx serology, n = 32</td>
<td>R-/D+ or R+/D+ serology, n = 244</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>RR 0.64 (95% CI, 0.36 to 1.16)</td>
<td>Low power, did not achieve significance</td>
</tr>
<tr>
<td>Conti 1996</td>
<td>Gan versus no Rx</td>
<td>Renal, R-/D+ only, n = 51</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>Decrease in RR</td>
<td>Abstract only, but reviews 126 patients who were given ganciclovir</td>
</tr>
<tr>
<td>Brennan 1997</td>
<td>Gan + IgG deferred Rx</td>
<td>Renal, R+ or R-/D+ serology, n = 42</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>RR 0.35 (95% CI, 0.14 to 0.88)</td>
<td>Low power</td>
</tr>
<tr>
<td>Snyderman 1987</td>
<td>IgG versus no Rx</td>
<td>Renal, unspecified serology, n = 99</td>
<td>Yes</td>
<td>Single</td>
<td>± ALG</td>
<td>RR 0.35 (worst and best case CI, 0.19 to 1.75)</td>
<td>Methodologic weakness: 40 patients excluded postrandomization</td>
</tr>
<tr>
<td>Glowacki 1994</td>
<td>IgG versus nil</td>
<td>All solid organ tx patients, 18 studies</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Odds ratio 0.58 (95% CI, 0.42 to 0.77)</td>
<td>Meta-analysis; includes many studies with weak design</td>
</tr>
<tr>
<td>Snyderman 1993</td>
<td>IgG versus placebo</td>
<td>Liver, any serology n = 141</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>RR 0.39 (95% CI, 0.017 to 0.089)</td>
<td>Level 1 evidence</td>
</tr>
<tr>
<td>Metselaar 1989</td>
<td>IgG versus placebo</td>
<td>Renal, all serologic gps, ± ALG n = 40</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
<td>RR 1.23 (95% CI, 0.50 to 2.99)</td>
<td>Small study, showed reduction in death rate but no difference in rate of infection (chance finding)</td>
</tr>
<tr>
<td>Gregor 1986</td>
<td>HI-IgG versus nil</td>
<td>Renal, all serology, n = 48</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>RR 1.16 (95% CI, 0.46 to 2.96)</td>
<td>Small study with factorial design</td>
</tr>
<tr>
<td>Fassbinder 1986</td>
<td>HI-IgG versus IgG</td>
<td>Renal, all serology, n = 74</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>RR 1.19 (95% CI, 0.82 to 1.73)</td>
<td>Small study</td>
</tr>
<tr>
<td>Steinmiller 1990</td>
<td>IgG versus nil</td>
<td>Renal, R+, n = 34</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>RR 0.02 (95% CI, 0.0 to 9.36)</td>
<td>Small study, unblinded</td>
</tr>
<tr>
<td>Balfour 1989</td>
<td>Acyclovir p.o. versus placebo</td>
<td>Renal, all serology, ALG</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
<td>RR 0.26 (95% CI, 0.09 to 0.75)</td>
<td>Level 1 evidence</td>
</tr>
<tr>
<td>Kletzmyr 1996</td>
<td>Acyclovir p.o. versus nil</td>
<td>Renal, R-/D+, n = 32</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>RR 1.02 (95% CI, 0.41 to 2.54)</td>
<td>Negative study, low power</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Follow-up</td>
<td>RR (95% CI)</td>
<td>Notes</td>
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<tr>
<td><strong>Practice</strong></td>
<td></td>
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<tr>
<td>Carri 1995</td>
<td>Acyclovir p.o. versus acyclovir and IgG, Renal, R-/D+ n = 116</td>
<td>No</td>
<td>No</td>
<td>Decrease in RR</td>
<td>Different immunosuppressives used; cohort design with nonconcurrent controls (level 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hopt 1994</td>
<td>Gan versus no Rx, Kidney/pancreas, n = 70</td>
<td>No</td>
<td>No</td>
<td>Nil</td>
<td>Nonrandomized, low power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh 1995</td>
<td>Gan versus IgG versus placebo, Repeat renal transplants</td>
<td>No</td>
<td>No</td>
<td>Nil</td>
<td>Nonrandomized, low power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merigan 1992</td>
<td>Gan versus no Rx, Heart, any serology, n = 149</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
<td>Stopped on interim analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacDonald 1995</td>
<td>Gan versus placebo, Heart, all serology, n = 56</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
<td>Level 1 evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aguado 1995</td>
<td>Gan versus IgG, Heart, R+ serology only, n = 31</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>Low power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakazato 1993</td>
<td>Gan + IgG versus acyclovir + IgG, Liver, any serology, n = 104</td>
<td>Yes</td>
<td>No</td>
<td>±FK506 ±ALG</td>
<td>Concurrent FK506 trial; at the time of discharge, all patients switched to acyclovir p.o.; weak design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winston 1995</td>
<td>Gan versus acyclovir p.o., Liver, any serology, n = 250</td>
<td>Yes</td>
<td>No</td>
<td>±ALG</td>
<td>Level 1 evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin 1994</td>
<td>Gan + acyclovir versus acyclovir, Liver, any serology, n = 143</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>Level 1 evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gane 1997</td>
<td>Gan versus placebo, Liver, excluded R-/D- serology, n = 304</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>Level 1 evidence, oral preparation of ganciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunn 1994</td>
<td>Acyclovir p.o. or i.v. versus Gan + IgG, All solid organ tx patients, n = 311</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
<td>Different organs and immunosuppressive therapy used, heterogeneous population; longer treatment duration in acyclovir group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Results are expressed as relative risk with 95% confidence intervals where possible. Gan, ganciclovir intravenously; Rx, therapy; ALG, antilymphocyte globulin; Nil, none; RR, relative risk; CI, confidence interval; SE, side effects; IgG, immunoglobulin (unspecified or pooled); HI-IgG, hyperimmune immunoglobulin; tx, transplantation; p.o., postoperatively; i.v., intravenously.
less of pretransplant serologic status, an overall reduction in risk of disease (RRR, 0.74; 95% CI, 0.25 to 0.91) was seen when oral acyclovir was administered over 12 wk to renal transplant patients (37). Although the study was randomized and placebo-controlled, 14 of the 118 patients initially randomized were excluded from the analysis. Thus, the treatment effect (measured as an RRR) can be recalculated, using both worst case and best case scenarios, to lie between 0.33 and 0.83 (NNT, 3.1 to 11.8).

Although the treatment benefit from Balfour’s study is impressive, the only study able to confirm these results was published by Dunn et al. (35). In this study, patients with any solid organ transplant were randomized to either a 12-wk course of oral acyclovir or a 7-d course of intravenous ganciclovir and immunoglobulin. A lower risk of disease was seen in those given acyclovir (RR, 0.65; 95% CI, 0.42 to 0.99); however, it is unclear if this was because of the longer duration of treatment with acyclovir or because acyclovir therapy was indeed superior to the combination of ganciclovir and immunoglobulin therapy.

Skepticism concerning the use of acyclovir is supported by the results published by Winston et al. (40) and Martin et al. (41). Both show that treatment with intravenous acyclovir followed by oral acyclovir, in liver transplant patients, is inferior to treatment with intravenous ganciclovir. These studies are discussed in the section, “Direct Comparisons Between Available Interventions.”

Ganciclovir

Ganciclovir (9-1,3-dihydroxy-2-propoxymethyl guanine, or DHPG) is a guanosine analogue similar in chemical nature to acyclovir, which has excellent in vitro activity against CMV. It is phosphorylated by virally infected cells to DHPG-triphosphate, a compound that inhibits DNA polymerase activity (46). Although first used in uncontrolled studies (47-49) for the management of severe systemic CMV infections, intravenous ganciclovir is now standard treatment for symptomatic patients. Prophylaxis, with intravenous and oral ganciclovir, has been shown to be of benefit in three randomized controlled studies (50-52) (and in a subsequent study as yet reported only in abstract form [53]) in the renal transplant population (level I evidence). Most patients studied were simultaneously treated with antilymphocyte products. The largest and most supportive trial was published in 1995 by Hibberd et al. (50). Recruitment was limited to patients who were seropositive for CMV before transplantation and who received antilymphocyte globulin (ALG) during the early course of transplantation (either for induction or for treatment of steroid-resistant acute rejection).

In this well designed, but unblinded study, 113 patients were randomized to receive either intravenous infusions of ganciclovir for a median of 9 d or no prophylactic therapy. Although cointervention was present in nine patients because of simultaneous therapy with acyclovir, the effects of this were minimized by randomization. The results showed a reduction in RR by 0.54 (95% CI, 0.27 to 1.00) of CMV disease (odds ratio 0.33 with treatment; NNT, 4.5). After adjustment for different dosing regimens of ALG and other relevant factors, the RR fell to 0.21 (95% CI, 0.12 to 0.64). Tissue invasive disease was also less common in those treated with intravenous ganciclovir, but because of a lower prevalence 15 patients required treatment for every case prevented (odds ratio, 0.53; NNT, 14.3). Furthermore, the results showed consistent trends from subgroup analysis, with the intervention causing a decrease in the occurrence of viremia, an increase in the time between transplantation and detectable viremia, and a delay in the onset of CMV disease. In addition, subgroup analysis of patients treated with intravenous ganciclovir during ALG therapy for steroid-resistant acute rejection also showed a decrease in symptomatic disease. Similar risk reductions were demonstrated by Conti et al., 1995 (51) (RRR, 0.84; 95% CI, 0.35 to 0.96) and Brennan et al., 1997 (52) (RRR, 0.65; 95% CI, 0.12 to 0.86), although in both cases the study numbers were smaller and the 95% confidence intervals were wider.

In two other studies, by Rondeau et al., 1993 (54) and Conti et al., 1994 (55), different serologic groups were studied (R-/ D+). Neither study achieved statistical significance but both showed trends toward reduced rates of disease and delayed onset of disease with treatment. Both lacked significant power to conclusively demonstrate a benefit.

No evidence is available to either refute or support the role of ganciclovir prophylaxis in renal transplant patients treated with conventional immunosuppression (i.e., no antilymphocyte products). Prophylaxis with both oral and intravenous ganciclovir, however, has been shown to be of benefit in well designed randomized controlled trials in patients receiving heart and liver transplants and conventional immunosuppression (in which the prevalence of CMV disease is much higher) (40,56-58). From this evidence one may propose that a treatment effect would be seen, although the magnitude of effect may be less. An attempt at predicting the NNT for different prevalence rates of disease was made and is shown in Table 3. Serious side effects of ganciclovir are infrequent and include

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<td>Baseline Risk of CMV Infection</td>
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* This table gives the number needed to treat, i.e., the estimated number of patients who will require treatment (unnecessarily) for each case of infection that is prevented. Assuming that the increase in cost for each case of CMV is $225,302 (10) and the cost of 2 wk of prophylaxis with ganciclovir is $1966.12, 12 patients can be treated with prophylaxis without additional expense. This is represented by the area below the heavy line.
bone marrow suppression, deterioration of renal function if high doses are given, and, on occasion, allergic reactions. No long-term or serious side effect has been reported, and the intervention can be considered safe.

Other Drugs Currently Available

Valaciclovir and famciclovir are newer formulations, similar in chemical structure to acyclovir (59). Valaciclovir is the L-valyl ester prodrug of acyclovir. The bioavailability of acyclovir, after the administration of valaciclovir, is almost 3 to 5 times greater than serum concentrations achieved after oral dosing with acyclovir. To date, valaciclovir is approved only for the treatment of herpes zoster and recurrent genital herpes in immunocompetent adults. Infection with CMV requires higher oral concentrations of acyclovir than for other herpes viruses to prevent viral replication. However, in a multi-centered randomized placebo-controlled trial in renal transplant patients (published in abstract form only), the administration of 8 g/d of valaciclovir prophylaxis was shown to reduce the risk of laboratory-confirmed CMV disease from 5 to 1% (RR, 0.19; 95% CI, 0.042 to 0.854) (60–62). Subgroup analyses showed similar results with few side effects.

Direct Comparisons Between Available Interventions

Few studies have actually compared the effectiveness of different treatment regimens in the renal population. The RRR seen with acyclovir and ganciclovir seem similar, although the studies were performed in different treatment populations and used different criteria for disease. However, four randomized control studies in liver transplant patients (three of which are of high quality) compare acyclovir, either in combination with IgG or alone, to ganciclovir (40–42,63). Three of the four studies show ganciclovir to be more effective than acyclovir (40,41,63), whereas the fourth (42) shows that acyclovir has a better prophylactic effect (RR 0.65 with acyclovir; 95% CI, 0.42 to 0.99) than ganciclovir. One possible reason for the discrepancy is that the latter study varied not only the type of therapy but the duration over which it was given. By extrapolation of the data from these four studies, one may expect that intravenous ganciclovir therapy will be superior to acyclovir in the renal population; however, this remains unproven. The efficacy of immunoglobulin therapy alone has not been directly compared with that of either acyclovir or ganciclovir. Although intravenous ganciclovir was chosen as the treatment of choice by the consensus group, this was based solely on the fact that a treatment effect was consistently demonstrated in more than one methodologically sound study.

Duration, Route, and Timing of Administration of Prophylaxis

Prophylaxis may be administered either at the time of induction or at the earliest sign of active viremia. The latter method, often termed preemptive therapy, assumes that active viral replication is easily and quickly detectable and correlates closely with symptomatic infection.

In a study of preemptive ganciclovir therapy, Brennan et al. (64) were unable to show any cost savings with preemptive therapy in a high-risk population. In this study, patients were intensively screened for CMV infection using pretransplant serology, shell vial technique, conventional culture, and PCR. Viremia was detected in 94% of patients, with sensitivity levels of 91, 44, and 47% for PCR, shell vial, and culture, respectively. Patients with detectable viremia in the preemptive group were treated with ganciclovir before any clinical manifestation, whereas those in the control group were treated only when clinical symptoms became evident. In six of 15 cases in the preemptively treated group, CMV infection became clinically evident (four despite previous preemptive therapy). In the control group, 13 of 21 patients developed clinically significant disease and required therapy with ganciclovir. No patients died and no difference was seen in the number and duration of CMV-related or non-CMV-related hospitalization in either group. Although the power and sample size of the study was small, the authors concluded that preemptive therapy was not cost-effective. Thus, prophylactic therapy administered at the time of induction remains the preferred method. In a subsequent study, Brennan et al. (52) compared oral ganciclovir prophylaxis over a 12-wk period with a preemptive regimen in a randomized controlled trial. The results confirmed their previous recommendations against the cost effectiveness of preemptive strategies.

The duration of therapy is also the subject of debate. Comparison of data across different studies in solid organ transplant recipients suggests that a longer duration of therapy may be more effective; however, this premise has not been examined in a formal study. Theoretically, it makes sense to give a longer course of therapy, because epidemiologic studies show that patients are at maximal risk of CMV disease for the first 4 mo after transplantation. In practice, however, the data even show benefits with short-term (2 wk) ganciclovir therapy (9,50,51,53,65) when given with antilymphocyte products. Thus, the consensus group recommend prophylaxis with at least 10 to 14 d of intravenous ganciclovir (i.e., during the administration of antilymphocyte products), a 12-wk course of oral acyclovir, or a 16-wk course of immunoglobulin therapy.

To be effective, prophylaxis must be convenient for the patient to take. Thus, oral therapy, taken preferably for a few days or weeks, is the most practical treatment regimen. Both acyclovir and ganciclovir are available in oral and intravenous formulations. Recent level 1 evidence has shown that oral ganciclovir is effective in both renal and liver transplant patients (52,66,67). In contrast, immunoglobulin therapy must be given intravenously.

Combination Therapy

Although advocated by some (68), there is little evidence to support the simultaneous use of two or more drugs. In the liver transplant population, two studies have compared combination therapy with use of a single agent. The results are contradictory: the first study shows better prophylaxis with a 3-mo course of acyclovir than a 7-d course of ganciclovir and hy-
perimmune globulin (42), and the second study shows improved results with ganciclovir used in combination with acyclovir (41). In the latter study, a 2-wk course of ganciclovir supplemented by 10 wk of oral acyclovir was compared with a 12-wk period of oral acyclovir. In a subsequent observational study in renal transplant patients, Martin et al. treated patients with a 2-wk course of ganciclovir, followed by a 10-wk period of oral acyclovir and hyperimmune globulin (68). Disease rates were encouragingly low, but because no comparative group was included, few conclusions can be drawn (type III evidence). Other retrospective nonrandomized or cohort studies (34) have also shown a trend to low disease rates with different combinations of drugs, but none confirms additional benefit to monotherapy.

Cost Implications

Cost efficacy studies in this area are greatly needed. In a retrospective case-controlled study, the cost of CMV disease was reported. The study showed higher mean total institutional costs, calculated in 1997 Canadian dollars for patients with CMV disease than for control subjects ($42,611 versus $17,309, \( P = 0.001 \)). The main differences were in costs attributable to inpatient care ($19,988 versus $7484, \( P = 0.001 \)), laboratory and radiology costs ($7001 versus $3198, \( P = 0.01 \)), and pharmacy expenses ($4916 versus $1782, \( P = 0.01 \)). No attempt to calculate the effectiveness of intervention was made. Nevertheless, the consensus group proposed that the potential savings from a cheap but effective therapy would be large (Table 3).

Conti et al. (55) report lower costs with the use of intravenous ganciclovir than with immunoglobulin; however, they include only pharmacy costs, and no attempt is made to estimate the cost associated with the administration of the drug, patient-incurred costs (travel, lost work time), or other costs of medical care.

In a cost effectiveness study, Tsevat et al. (69) used a decision analysis model to evaluate the cost of saving a life using immunoglobulin therapy. They demonstrate an incremental cost of therapy as the risk of infection falls. For example, the cost of administering therapy to a CMV seronegative recipient of a seronegative donor is estimated at $1.68 million (US) per life saved, whereas that of a CMV seronegative recipient receiving an organ from a seropositive donor is $29,800 (US).

The current estimate of the cost of a 2-wk course of intravenous ganciclovir is $1966.12 (CAN) ($1366.12 for the drug and $600 for administration supplies). Assuming that hospital costs for one case of CMV average $25,302 (CAN) (12), cost equivalency would be achieved if 12.9 patients were given prophylaxis for each case of CMV prevented. Table 3 shows the NNT for different prevalence rates of CMV disease and for different efficacy levels for treatment. For example, in a population similar to that of Hibberd et al. (50), treated with a 2-wk course of intravenous ganciclovir with a treatment efficacy of 50%, only three patients would need to be treated to prevent one case of CMV disease. This value is well below the cost effectiveness number (calculated above as 12.9), and therefore one would suggest that prophylaxis with ganciclovir is the optimal choice. The heavy black line is drawn to show the cost-effective cutoff points. Any value below this line has benefit for both the patient and the service provider (Table 3).

Recommendations of Other Bodies

No evidence-based guidelines have been published in this area. In 1995, a distinguished group of researchers in the field of CMV therapy collectively published the therapeutic protocols being used for all solid organ transplants in their own centers (71). No assessment was made of the quality of the literature. In a systematic review published last year by Dickinson et al. (72), the different studies were assessed and interpreted using evidence-based principles; however, guidelines for patient management were not drafted.

Future Directions

Further research is required in the treatment of CMV after renal transplantation. Inconsistent definitions and diagnostic variability across studies have made it difficult to interpret the results and are areas that would benefit from clarification. Other unresolved issues include the most optimal duration of prophylactic therapy and the use of combination protocols. To date, these questions remain unanswered, and only continued research in this field will provide the long-term solutions needed.

Recommendations

(1) Seropositive Recipient; Donor Seropositive or Seronegative; Immunosuppression with Antilymphocyte Products

Prophylaxis with Antiviral Therapy Recommended (Grade A Recommendation). This recommendation is based on strong evidence from three type 1 studies (37,50,51) (two high quality, one of low quality) in renal transplant patients. Supportive evidence also comes from five randomized clinical trials in other solid organ transplant patients (40,42,56–58). The drug of choice remains unknown, because no comparative studies in renal transplant patients have been done; however, based on the quality of the studies and supportive evidence from liver and heart transplant patients, prophylaxis with oral or intravenous ganciclovir for a minimum 14-d period is recommended.

(2) Seronegative Recipient; Seropositive Donor; Immunosuppression with Antilymphocyte Products

Prophylaxis with Antiviral Therapy Recommended (Grade A Recommendation). This recommendation is based on data from two randomized clinical trials in R-/D+ renal transplant patients (37,54) and on results extrapolated from studies in R+/D± patients (50,51). Further supportive evidence comes from type 1 studies in heart and liver transplant patients (40,42,56–58). Studies demonstrate benefit from both oral acyclovir and oral and intravenous ganciclovir, although no head-to-head comparison trial has been done in renal
transplant recipients. On the basis of evidence from a comparative trial in liver transplant recipients (40), ganciclovir (for a minimum 14-d period) is proposed as the drug of choice.

(3) Seronegative Recipient; Seropositive Donor; Conventional Immunosuppression

Prophylaxis with Antiviral Therapy Recommended (Grade B Recommendation). This recommendation is based on weak evidence in support of the use of prophylactic antiviral medication. The risk of disease is estimated at 10 to 40% depending on the series reviewed (11,12,17,73–76). Only one randomized controlled trial of immunoglobulin has been done specifically in this population (19), but because of the high exclusion rate, postrandomization, conclusions are indeterminate.

(4) Seronegative Recipient; Seronegative Donor; Any Immunosuppressive Regimen

No Prophylaxis with Antiviral Therapy Required (Grade D/E Recommendation). On the basis of multiple observational and cohort studies (11,12,17,37,40,73–76) showing a low prevalence of disease, therapy is not recommended (grade E). No trials of treatment have been carried out specifically in this population (grade D).

(5) Seropositive Recipient; Donor Seropositive or Seronegative; Conventional Immunosuppressive Regimen

Prophylaxis Left to the Discrimination of the Physician in Charge (Grade C Recommendation). There is minimal evidence for or against treatment in this population because few studies have examined the effect of different treatment regimens. In liver transplant recipients, the efficacy of treatment is less in R+ patients than in R−/D+ patients or in patients receiving antilymphocyte products (40). Subgroup data from Balfour et al. (37) suggest a benefit, but the strength of the data is insufficient to make a recommendation for therapy. Geographical variation in susceptibility may influence the decision: If one assumes the efficacy is similar to that reported for transplant recipients with different serostatus pretransplantation, the number needed to treat can be calculated for different disease prevalence rates (Table 3).

References
23. Snyderman DR, Werner BG, Dougherty NN, Griffith J, Rohrer