Preemptive Therapy Versus Universal Prophylaxis with Ganciclovir for Cytomegalovirus in Solid Organ Transplant Recipients

Nina Singh
Veterans Affairs Medical Center and University of Pittsburgh, Thomas E. Starzl Transplantation Institute, Pittsburgh

Whether preemptive therapy or universal prophylaxis with ganciclovir is the optimal approach against cytomegalovirus (CMV) remains unresolved. Controversy abounds with respect to the efficacy of preemptive therapy, the reliability of preemptive therapy tools, the logistical difficulties in conducting surveillance monitoring for CMV, the cost of prophylaxis, the effect of prophylaxis on indirect sequelae of CMV and epidemiology of CMV, and the potential for emergence of ganciclovir-resistant CMV. Although neither approach is wholly adequate, a discussion of the relative merits and limitations of the 2 approaches may guide the selection of a rational approach toward prevention of CMV infection in organ transplant recipients.

Cytomegalovirus (CMV) has long been recognized as the most common opportunistic pathogen in transplant recipients [1–3]. Although prophylaxis with ganciclovir has undoubtedly been associated with a substantial decline in CMV-associated morbidity, an optimal approach to treatment and how best to utilize ganciclovir for prophylaxis remain controversial and unresolved.

First, a brief description of the terminology used to describe various approaches to CMV prophylaxis would be relevant. "Universal prophylaxis" involves administration of ganciclovir, usually for a prolonged period, to all transplant recipients, irrespective of the risk of CMV disease. A major limitation of this approach is that most patients, while incurring the cost, toxicity, and risk for emergence of resistance, are unlikely to benefit from prophylaxis. "Preemptive therapy" involves directing prophylaxis only toward high-risk transplantation recipients (e.g., patients in whom early replication of CMV occurs) in an attempt to prevent the progression of asymptomatic infection into CMV disease. The term "early treatment" has also been used to describe this strategy [4].

Although the concept of preemptive therapy is appealing, it faces criticism with regard to its efficacy, the logistics and cost of surveillance monitoring, and the potential failure to prevent indirect sequelae of CMV infection. "Targeted prophylaxis" involves administration of ganciclovir to a subset of high-risk patients (e.g., patients who are receiving antilymphocytic preparations for rejection) before viral replication ensues [4]. The efficacy of this approach has been amply documented, and it is not controversial [5, 6]. However, controversy abounds regarding universal versus preemptive therapy as an optimal prophylaxis against CMV infection in organ transplant recipients.

This discussion pertains to the relative merits and limitations of either universal or preemptive therapy for the prevention of CMV disease in solid organ transplant recipients, with regard to the following controversies and uncertainties: Is preemptive therapy effective? Are currently available tests for diagnosis of CMV infection reliable tools for preemptive therapy? Do the logistics of surveillance monitoring represent a practical limitation of preemptive therapy? Are the 2 approaches comparably cost-effective? Does prophylaxis affect indirect sequelae of CMV infection? What are the adverse effects associated with prophylaxis? Has prophylaxis altered the epidemiology of CMV infection? Is there significant potential for emergence of ganciclovir-resistant CMV with the 2 approaches?

Data on each of the aforementioned issues are presented here. While neither strategy can be considered ideal at the
present time, such data can lead to the selection of a rational approach in discerning the appropriate strategy for use of ganciclovir therapy to prevent CMV infection in organ transplant recipients.

**IS PREEMPTIVE THERAPY EFFECTIVE?**

The conceptual principles that form the basis for preemptive therapy are that it is targeted toward high-risk patients, is timed to be maximally effective in aborting impending disease, and is administered for a defined, usually short duration. The first question, however, is whether preemptive therapy is effective and whether its efficacy is comparable to that of universal prophylaxis.

In a randomized trial that involved predominantly seropositive patients, universal prophylaxis with iv ganciclovir that was administered to patients for 100 days after they had undergone liver transplantation was associated with a CMV disease rate of 1% among all patients and 10% among those at risk for primary CMV infection (seronegative recipients of seropositive allografts) [7]. However, the approach to treatment did not gain wide acceptance because of the requirement of prolonged iv administration of the drug [7]. Instead, long-term administration of oral ganciclovir has emerged as the most widely employed form of prophylaxis at most transplantation centers. Administration of oral ganciclovir for 100 days reduced the rate of CMV disease to 5% among all patients and to 15% among those at risk for primary CMV infection [8].

A number of studies, including those involving high-risk transplant recipients, have documented that preemptive therapy can lead to a reduction in the rate of CMV disease comparable to that of treatment with universal prophylaxis [9–15]. Although the studies were limited by their small sample sizes [10, 11, 15] or uncontrolled designs [11, 15], they still showed that preemptively administered ganciclovir was associated with CMV disease rates of zero to 6% [9–12, 14, 16–18]. In addition, only 22%–55% of the patients in these studies required prophylaxis.

Emerging data about preemptively administered oral ganciclovir also appear promising. In seropositive liver transplant recipients for whom treatment with oral ganciclovir (3 g/d) was initiated when antigenemia became detectable, and which was continued until antigen levels had remained negative for 7 days, a rapid decline in CMV antigenemia was observed [19]. In another study [20], of 15 seropositive liver transplant recipients had CMV DNA detectable in plasma for 2 consecutive weeks or had CMV DNA in a single plasma sample, with a virus load of $>3 \times 10^4$ genomes/mL. Prophylaxis with oral ganciclovir (dosage, 3 g/d for 12 weeks, employed preemptively) led to undetectable CMV DNA levels in all patients after 2 weeks of treatment [20]. None of the patients who received oral ganciclovir in both of the aforementioned studies developed CMV disease.

Antiviral therapy in patients with high virus burden (e.g., in patients at risk for primary CMV infection) not only may be ineffective, but may promote the emergence of drug-resistant CMV [21, 22]. However, in patients with low-level viremia that is detectable by use of closely monitored surveillance tests, preemptively administered oral ganciclovir was uniformly effective in aborting asymptomatic CMV infection, even in patients with primary CMV infection [18]. Of equal importance, 69% of the patients never had detectable CMV antigenemia throughout the monitoring period, and, therefore, they did not receive any prophylaxis; CMV disease developed in none of these patients [18]. Thus, the negative predictive value of the CMV antigenemia test was 100% and the need for (unnecessary) antiviral prophylaxis was eliminated for a vast majority of the study patients. Treatment with oral ganciclovir that was administered to patients who had positive results on CMV PCR was associated with a significant reduction in the CMV infection rate among all study patients, including seronegative recipients who received hepatic allografts from seropositive donors [23].

There are no unique differences between renal, heart, and liver transplant recipients with respect to reliability of preemptive or universal prophylaxis. In these subgroups of transplant recipients, CMV disease is largely preventable with use of either approach. However, prophylaxis for CMV disease in lung transplant recipients has proven to be particularly challenging, given an overall greater degree of immunosuppression in these patients. CMV disease rates of 28%–42% have been documented in this subgroup of patients, despite universal prophylaxis with iv ganciclovir [24–26].

Only 2 published reports of studies of treatment with preemptive iv ganciclovir have involved lung transplant recipients [27, 28]; a historical control group was used for comparison in both studies. Preemptive therapy was associated with a significant reduction in CMV disease when compared with rates among patients who did not receive ganciclovir prophylaxis; there were no treatment failures in patients who received preemptive therapy [27]. In another study report, the incidence of CMV disease in patients who received preemptive prophylaxis [26%] was comparable to that in patients who received universal prophylaxis [38%] [28]; this study, however, did not employ histologic criteria for the diagnosis of CMV pneumonitis [28].

Data on the use of oral ganciclovir therapy for lung transplant recipients are largely lacking. Indeed, the absorption of oral ganciclovir is potentially a concern for patients with cystic fibrosis, who account for a significant proportion of patients undergoing lung transplantation [29]. A pharmacokinetic study, however, documented adequate levels in these patients after the administration of oral ganciclovir [29]. In a study that has been published only in abstract form thus far [30], lung
transplant recipients received iv ganciclovir for 8–21 days, followed by oral ganciclovir (1 g t.i.d.) until 90 days after transplantation. The incidence of CMV disease and the survival rate at 90 and 180 days did not differ between the group that received oral ganciclovir and a historical control group that received iv ganciclovir thrice weekly for 90 days [30]. Nevertheless, the administration of oral ganciclovir to lung transplant recipients should be observed in further clinical trials.

A report from the working party of the British Society for Antimicrobial Chemotherapy on the management of herpesvirus infections in transplant recipients considered preemptive therapy to be a category 1 recommendation (evidence from at least 2 randomized, controlled trials) for liver and kidney transplant recipients and a category 2 recommendation (evidence from at least 1 randomized, controlled trial) for lung transplant recipients [31].

**ARE RELIABLE PREEMPTIVE THERAPY TOOLS CURRENTLY AVAILABLE?**

Failure of conventional diagnostic tests that are based on cytopathology to rapidly and reliably detect CMV infection has been a severely criticized limitation of the preemptive therapy approach [32, 33]. However, the newer tests, which are based on CMV antigen and genome detection methodology, have revolutionized the approach to early diagnosis of CMV infection and have rendered the risk-adapted approach to antiviral therapy highly efficient and effective. Diagnosis of CMV antigenemia is based on the detection of nucleoprotein pp65 of the CMV virion, detected by use of monoclonal antibody staining of peripheral blood leukocytes [34–36]. Granulocytes are believed to be infected by CMV in the process of viral dissemination. A sensitivity for this assay of 94%–100% and a specificity of 76%–94% for CMV infection has been documented [35, 37, 38].

CMV antigenemia was associated with a positive predictive value of 94% for the early detection of CMV disease [38]. The test is easy to perform, has a rapid turnaround time, and can be quantitated. A number of studies that involved bone marrow and solid organ transplant recipients have validated antigenemia detection as a reliable tool for preemptive therapy [14, 17, 18, 27, 39]. Potential disadvantages of the antigenemia test include the need for immediate processing of specimens and the requirement of a leukocyte count of ≥200 cells/μL for performance of the test.

Detection of CMV DNA in the leukocytes by use of the highly sensitive PCR obviates the need for immediate processing of samples, and yields the greatest lead time before the onset of CMV disease. Qualitative PCR, however, may not distinguish latent CMV infection from replicating CMV infection. Detection of CMV DNA by means of PCR in plasma or serum and CMV RNA (mRNA) is considered specific for replicating virus [40, 41]. These tests, however, are technically challenging and are not routinely available, and experience with them in clinical trials has been limited. Their sensitivity and specificity have been reported to be identical to those of the antigenemia test [42].

The CMV DNA level (also referred to as virus load), determined by means of quantitative PCR, has been shown to correlate with CMV disease and to predict late-onset relapsing infection [43–47]. At present, preemptive therapy for transplant recipients may be based on results of the antigenemia test or quantitative PCR, depending on access to the tests. The novel application of PCR technology (e.g., to determine rate of increase in virus load [log_{10} genomes/mL/d]) may refine the identification of transplant recipients at high risk for CMV disease [48].

**ARE LOGISTICS OF SURVEILLANCE MONITORING A PRACTICAL LIMITATION OF THE PREEMPTIVE THERAPY APPROACH?**

The success of preemptive therapy hinges upon the early detection of CMV infection. Consequently, efficient surveillance monitoring is a crucial component of the preemptive therapy approach. The logistics of conducting surveillance tests, however, are perceived by many as a major barrier to the implementation of preemptive therapy. Indeed, obviating the need for monitoring is often the primary reason why many transplantation centers prefer to administer universal instead of preemptive prophylaxis. However, resorting to unnecessary treatment with drugs merely for the sake of convenience may not be appropriate.

A proposed solution to enhance adherence with surveillance monitoring protocols is to delegate the responsibility of monitoring to a dedicated transplantation coordinator rather than to physicians. In a report of a study in which clinicians were in charge, the rate of compliance with surveillance monitoring protocols was only 47% [49]. For centers that perform a large number of transplantations, hiring a dedicated transplantation coordinator (for a half- or full-time-equivalent position, depending on the size of the program) should be considered. The coordinator would be responsible for ordering the surveillance tests, ensuring that the samples arrive in a timely manner, retrieving the test results, and responding to the positive results by coordinating the arrangements for drug administration. The cost-savings that would result from administration of preemptive prophylaxis, despite compensation for the equivalent of a full-time coordinator, would outweigh the expenses associated with universal prophylaxis.

Weekly follow-up upon discharge is standard for patients who are early into the period after transplantation. Al-
though out-of-town patients may be able to undergo routine laboratory tests for chemistry and blood counts in their respective locales, blood samples for immunosuppressive drug monitoring (e.g., of tacrolimus and cyclosporine levels) are almost invariably transported to the primary transplantation institution. Collection and shipment of samples for CMV tests can be coordinated and integrated with the latter. A similar approach was implemented at our institution in the early 1990s, and it has now been in place for the past 10 years, with negligible resource utilization and virtually no imposition on the time of the transplantation coordinators.

**DOES PROPHYLAXIS AFFECT THE INDIRECT SEQUELAE OF CMV DISEASE?**

Given the growing recognition of adverse effects of indirect sequelae of CMV disease on outcome in transplantation cases, the efficacy of prophylaxis may no longer be relevant merely in the context of prevention of CMV disease; its impact on indirect morbidity associated with CMV is also important.

**Impact on medical resource utilization.** CMV has been associated with increased costs and prolonged hospitalization [50–52]. Carefully conducted analyses, however, have documented that higher resource utilization resulted from treatment of CMV disease [51] and that asymptomatic CMV shedding (viremia) was not associated with a significant increase in health care costs [51]. Indeed, the hospital charges incurred by patients with asymptomatic CMV infection (mean cost, $119,600) were similar to those for patients without CMV infection (mean cost, $114,100), and both groups had significantly lower charges than the patients with CMV disease (mean cost, $148,300; \( P < .01 \)). In the same study, a decrease in resource utilization with universal prophylaxis could only be documented for seronegative recipients of hepatic allografts from seropositive donors. For all other patients, universal prophylaxis did not lead to a reduction in charges [51].

Because preemptive therapy is meant to prevent CMV infection from progressing to CMV disease, it is likely that the potential benefits of prophylaxis on resource utilization could also be realized with use of preemptive therapy.

**Impact on opportunistic infections.** CMV is considered an immunodulatory virus, and it has been proposed that CMV infection leads to increased susceptibility to opportunistic infections [53–56]. However, it is not known whether CMV infection per se or symptomatic disease contributes to this risk (as was shown in a study that involved heart transplant recipients) [53]. Others have documented a higher risk of superinfections in patients with only primary CMV infection [56]. The association between CMV and superinfections could also be bidirectional, since sepsis due to either bacterial or fungal infections has been shown to lead to CMV infection via release of TNF- \( \alpha \) [57–59].

Prophylaxis against CMV has not uniformly been documented to lead to a decrease in superinfections. Despite nearly complete elimination of CMV by use of long-term administration of iv ganciclovir, no difference in the incidence of bacterial and fungal infections could be documented in liver transplant recipients [7]. Administration of prophylactic ganciclovir for 28 days (compared with placebo) led to a lower incidence of fungal infections among heart transplant recipients [60]. However, when late-onset infections (those occurring >1 year after transplantation, all of which happened in the control group) were excluded, the difference was no longer statistically significant [60].

A comparison of the preemptive and universal prophylactic approaches has not been conducted with regard to solid organ transplant recipients. However, in a study that involved bone marrow transplant recipients in which antigen-guided preemptive ganciclovir was compared with universal ganciclovir prophylaxis at engraftment, the prophylactic ganciclovir recipients had a significantly higher incidence of invasive fungal infections and were more likely to die from nonviral infections than were patients in the preemptive therapy group [9].

**Impact on rejection.** Theories regarding an association between CMV and allograft rejection have long been proposed [61–63], and reduction in the risk of rejection with valacyclovir prophylaxis has recently been documented in a study that involved renal transplant recipients [64]. Most such studies, however, were conducted prior to the 1990s, when CMV infection could be detected only by use of unsophisticated diagnostic tools, such as cytopathology. Consequently, the correlation between the precise characteristics of CMV infection (e.g., virus load and duration of viremia) and rejection remains poorly defined. The study by Evans et al. is laudable in this regard [65]; CMV infection, symptomatic CMV infection, and peak/cumulative virus load were not predictive of chronic rejection of transplanted organs in liver transplant recipients. Instead, prolonged subclinical CMV infection, as detected by use of PCR, was the most significant predictor of chronic rejection [65].

Whether preemptive therapy can accomplish the goal of curtailing rejection by aborting early subclinical infection remains to be determined. However, the data by Evans et al. suggest that this is biologically plausible.

**Impact on posttransplantation atherosclerosis.** Researchers have suggested that CMV plays a role in the acceleration of coronary atherosclerosis in cardiac allograft recipients [66–68]. A post hoc analysis (mean duration of follow-up, 4.7 years) of a randomized study that was designed to assess the efficacy of ganciclovir, given for 28 days, as com-
Table 1. Clinical characteristics of organ transplant recipients with ganciclovir-resistant cytomegalovirus (CMV).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of transplant (n^a)</th>
<th>CMV serostatus of recipient (R)/donor (D)</th>
<th>Prior antiviral agent(s) received</th>
<th>CMV disease</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[22]</td>
<td>Liver (1)</td>
<td>R^+/D^+</td>
<td>CMV Ig, Acy, and 3 courses of iv Gan</td>
<td>Gastritis</td>
<td>Foscarnet</td>
<td>Alive</td>
</tr>
<tr>
<td>[86]</td>
<td>Lung (1)</td>
<td>R^+/D^+</td>
<td>Acy, 3 courses of iv Gan</td>
<td>Retinitis</td>
<td>Foscarnet</td>
<td>Died</td>
</tr>
<tr>
<td>[87]</td>
<td>Heart (1)</td>
<td>R^+/D^+</td>
<td>3 courses of iv Gan, followed by 2 mo of oral Gan</td>
<td>None</td>
<td>Foscarnet</td>
<td>Alive</td>
</tr>
<tr>
<td>[88]</td>
<td>Kidney (1)</td>
<td>R^+/D^+</td>
<td>4 courses of iv Gan, followed by daily maintenance iv Gan</td>
<td>None</td>
<td>Reduced IS</td>
<td>Alive</td>
</tr>
<tr>
<td>[89]</td>
<td>Liver (1)</td>
<td>R^+/D^+</td>
<td>22 d of iv Gan, followed by 3 mo of oral Gan</td>
<td>CMV syndrome</td>
<td>Foscarnet</td>
<td>Alive</td>
</tr>
<tr>
<td>[89]</td>
<td>Kidney (1)</td>
<td>R^+/D^+</td>
<td>26 d of iv Gan, followed by 3 mo of oral Gan</td>
<td>Retinitis</td>
<td>Intraocular foscarnet and CMV Ig</td>
<td>Alive</td>
</tr>
<tr>
<td>[74]</td>
<td>Liver, kidney, kidney-pancreas (5)</td>
<td>R^+/D^+</td>
<td>Oral Gan for a median of 129 d</td>
<td>NA</td>
<td>NA</td>
<td>Alive</td>
</tr>
<tr>
<td>[76]</td>
<td>Kidney, lung, heart (11)</td>
<td>R^+/D^+ (10/11^a^)</td>
<td>Oral Acy (6/11); 3/5 lung transplant recipients had received iv Gan 3 times per w</td>
<td>Tissue-invasive disease (9/11)</td>
<td>Foscarnet (4), protracted Gan (3); therapy not known for others</td>
<td>5/11 Died</td>
</tr>
<tr>
<td>[77]</td>
<td>Lung (18)</td>
<td>R^+/D^+ (8); R^+/D^- (6); R^-/D^- (4)</td>
<td>iv Gan for a mean of 75 d^b</td>
<td>CMV pneumonitis (a mean of 0.24 episodes/bronchoscopy)</td>
<td>Foscarnet (11/18), Gan (6/18); therapy not known for 1/18</td>
<td>9/18 Died</td>
</tr>
<tr>
<td>[90]</td>
<td>Kidney (1)</td>
<td>R^-/D^-</td>
<td>One course of iv Gan, followed by 2 mo of oral Gan</td>
<td>CMV syndrome</td>
<td>Decreased IS and polyvalent globulin</td>
<td>Alive</td>
</tr>
</tbody>
</table>

**NOTE.** Acy, acyclovir; Gan, ganciclovir; IS, immunosuppression; NA, not applicable.

^a Number of patients in the report.

^b Some patients had also received oral ganciclovir.

^c Duration of survival of patients infected with ganciclovir-resistant CMV was significantly shorter than that of other patients in the transplantation database.

pared with that of placebo for the prevention of CMV disease in heart transplant recipients showed that the actuarial incidence of posttransplantation coronary artery disease was significantly lower among patients who were treated with ganciclovir [68]. The incidence of coronary atherosclerosis was lower in seronegative recipients who were randomized to receive ganciclovir, as compared with seronegative recipients who were randomized to receive placebo. The incidence of posttransplantation coronary artery disease did not differ between seropositive recipients who were randomized to receive ganciclovir and placebo recipients. In the original trial of patients who received treatment with ganciclovir, however, a reduction in the prevalence of CMV disease was observed in the seropositive recipients but not in the seronegative recipients [69].

These data suggest that the effect of ganciclovir on coronary artery atherosclerosis may be independent of its inhibitory effect on viral replication or CMV disease. Indeed, a report of a study that involved an animal model suggested that ganciclovir may have a direct inhibitory effect on smooth-muscle replication [70]. In vitro data have documented a dose-dependent inhibitory effect of ganciclovir on smooth-muscle-cell replication, which indicates that the protection against enhanced graft atherosclerosis induced by ganciclovir may be mediated via pathways other than direct viral inhibition [70].

Studies of patients who did not undergo transplantation have suggested that mere CMV-seropositivity, even in the absence of active infection, may confer a risk for atherosclerosis [71]. Expression of immediate early gene products during an abortive CMV infection inhibits p53 function, and theories regarding their effect on inflammatory and immunologic responses in the absence of a lytic infection have been proposed [71].

A recent report documented that only prolonged CMV infection, defined as persistently positive buffy coat culture results over a 4-month period, was significantly predictive of cardiac allograft vasculopathy [72]. CMV infection, primary CMV infection, 4-month persistent CMV infection, and 6-month persistent CMV infection were not significantly associated...
with cardiac allograft vasculopathy [72].

The precise mechanism of ganciclovir’s protective effect and the characteristics of CMV (e.g., virus load and prior infection vs. asymptomatic vs. symptomatic disease) that influence its association with atherosclerosis need to be better delineated. Therefore, it would be premature to recommend either approach as the preferred strategy for the prevention of posttransplantation atherosclerosis.

**WHAT ARE THE ADVERSE EFFECTS OF PROPHYLAXIS?**

Neutropenia has been the most frequently reported side effect of ganciclovir therapy, and it has been notably larger in bone marrow recipients, as compared with solid organ transplant recipients. In bone marrow transplant recipients who received long-term treatment with ganciclovir, neutropenia was an independent predictor of poor survival, relapse, and non-relapse-related mortality for patients who underwent transplantation for acute myelogenous leukemia, and it was predictive of an increased risk for fungal and bacterial infections [73]. The frequency of development of neutropenia did not differ significantly between patients who received prophylaxis and those who received preemptive prophylaxis in a study of bone marrow transplant recipients [9]. However, the number of patients exposed to ganciclovir would, by necessity, be notably smaller with a preemptive approach that it would be with a universal prophylactic approach.

**HAS PROPHYLAXIS ALTERED THE EPIDEMIOLOGY OF CMV INFECTION?**

Symptomatic disease due to CMV has traditionally been observed in patients 4–6 weeks after they undergo transplantation, with virtually all cases occurring within 3 months. Emerging data suggest that universal prolonged prophylaxis may lead to a shift in the time course of CMV infection; transplant recipients may present with CMV disease and, in particular, ganciclovir-resistant CMV infection several months after they undergo transplantation. Prophylaxis has delayed the onset of CMV disease in transplant recipients [9, 25, 64, 74]. CMV disease that had occurred 10 months posttransplantation in kidney and kidney-pancreas transplant recipients who had received oral ganciclovir for a median of 129 days was due to ganciclovir-resistant CMV in 20% of the cases [74].

Existing data suggest that such a phenomenon may be less likely to occur in patients who receive preemptive therapy [9, 18]. In liver transplant recipients who received oral ganciclovir preemptively, no instances of late CMV disease were observed in patients who were followed for a median of 3 years and for up to 5 years [18]. Impaired reconstitution of CMV-specific T cell response in patients who receive prophylaxis has been proposed to account for late CMV disease [9]. Whether reconstitution of such a response is more efficient in patients who receive preemptive prophylaxis remains to be determined.

The prophylactic approach to treatment of CMV may also influence the epidemiology of nonviral infections in transplant recipients. A duration of ganciclovir treatment of >4 weeks was a significant predictor of not only late-onset CMV disease but also invasive aspergillosis [75]. In fact, each week of ganciclovir treatment increased the risk of invasive aspergillosis by a factor of 1.4 [75].

**ANTIVIRAL RESISTANCE**

Ganciclovir-resistant CMV has, thus far, been considered rare in patients who undergo transplantation. Recent data, however, suggest that, in the setting of suboptimal suppression and prolonged ganciclovir use, ganciclovir-resistant CMV may be emerging as a clinically relevant pathogen in transplant recipients (table 1). At one institution that employed prolonged prophylaxis with oral ganciclovir, 10% of the patients who underwent solid organ developed CMV disease within the first year after transplantation [74]. Of note, 20% of the patients with CMV disease had ganciclovir-resistant CMV [74]. At another institution, 11 infections with ganciclovir-resistant CMV in organ transplant recipients were documented; a majority of these patients had received prolonged oral ganciclovir prophylaxis [76].

Serious sequelae were documented in 4 of 5 kidney and kidney-pancreas transplant recipients with ganciclovir-resistant CMV disease, including permanent vision loss in 1 patient, allograft loss and resumption of hemodialysis in 2 patients, and deterioration of allograft function requiring relisting for transplantation in 1 patient [74]. In a study that compared the outcomes for lung transplant recipients infected with ganciclovir-resistant CMV with outcomes for matched controls and for other patients in the institution’s transplantation database, ganciclovir-resistant CMV infection was associated with significantly more episodes of viremia, more frequent disease, earlier onset of bronchiolitis obliterans, and shorter duration of survival [77]. In another report, 4 (100%) of the 4 patients with primary combined immunodeficiency who developed ganciclovir-resistant CMV disease after they underwent bone marrow transplantation died; clinical and histologic evidence of severe CMV disease was detected in all of them [78]. Of the organ transplant recipients with ganciclovir-resistant CMV disease who were described in another report [76], 5 (45%) of 11 died; 4 of the deaths were deemed related to CMV.

These data suggest that routine utilization of prolonged ganciclovir prophylaxis is fraught with substantial risk of the emergence of resistance, a scenario that has been amply documented in reports about the widespread utilization of other antimicrobial agents [79].
The data on analyses of cost-effectiveness of prophylaxis against CMV are strikingly scant. In a hypothetical cohort of liver transplant recipients, the cost-effectiveness of various strategies of universal prophylaxis were compared with use of the Markov model as a decision analysis tool [80]. Considering cost per patient, gain in quality-adjusted stages, amount of time spent in the state of CMV disease, and CMV-related mortality, universal administration of oral ganciclovir (compared with administration of universal iv ganciclovir, CMV Ig, and acyclovir) was the most cost-effective intervention [80]. It is unfortunate that the preemptive approach was not included in this model.

Two studies of liver transplant recipients have compared the cost of CMV antigenemia-guided preemptive treatment with that of universal prophylaxis [14, 18]. The total cost (including that of monitoring) of preemptive prophylaxis with iv ganciclovir, initiated upon detection of CMV antigenemia in 144 liver transplant recipients, was $69,068 [14]. It was estimated that if universal prophylaxis with iv ganciclovir, administered for 14 days, or oral ganciclovir, administered for 90 days, had been employed for these same patients, the costs would have totalled $100,676.16 and $621,691.20, respectively [14]. Preemptive treatment (including the expense of monitoring) in another study that involved liver transplant recipients entailed a theoretical savings of $118,759.20 ($1650 per patient; compared with the cost of universal iv prophylaxis) and a savings of $224,340 ($3115 per patient; compared with the cost of universal oral prophylaxis for 100 days) [18].

For seropositive allogeneic bone marrow transplant recipients, a preemptive plan (including tests and surveillance bronchoalveolar lavage) was projected to cost 44% less than would the prophylactic plan, with potential savings of $800,182 ($8001 per patient), assuming a sample size of 100 patients per group [81]. A net savings of $2569 per patient was documented with preemptive versus universal prophylaxis with iv ganciclovir for lung transplant recipients [28]. Thus, preemptive therapy, despite the expense of laboratory tests, was associated with lower costs than those of universal prophylaxis.

Cost-effectiveness, however, should not be determined on the basis of only direct drug-acquisition and surveillance-monitoring expenses, but the cost of accessing and maintaining an intravenous portal for drug administration and the costs for potential morbidity associated with the risk of catheter-related bactemia should also be considered. In addition, such analyses should reflect the “indirect” costs, including those associated with utilization of medical resources, management of adverse effects from prophylaxis, treatment of ganciclovir-resistant CMV disease, and the impact of indirect sequelae of CMV.

### SUMMARY

Commonly used ganciclovir prophylactic regimens are outlined in table 2. Current approaches to CMV prophylaxis are neither universally effective nor universally satisfactory. However, on the basis of this overview, the following strategies may be considered. For patients who are at risk for primary CMV infection (i.e., seronegative recipients of allografts from seropositive donors) neither strategy of prophylaxis is wholly adequate. Viral replication occurs predictably in these pa-

### Table 2. Cytomegalovirus prophylactic regimens of ganciclovir in selected studies involving organ transplant recipients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of transplant</th>
<th>Prophylactic approach</th>
<th>Prophylactic regimen and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>[8]</td>
<td>Liver</td>
<td>Universal</td>
<td>Gan, 1 g po t.i.d. (initiated within 10 d) for 98 d after transplantation</td>
</tr>
<tr>
<td>[7]</td>
<td>Liver</td>
<td>Universal</td>
<td>Gan, 6 mg/kg/d iv for 30 d, then 5 d/w for 70 d</td>
</tr>
<tr>
<td>[82, 83]</td>
<td>Liver</td>
<td>Universal</td>
<td>Gan, 5 mg/kg iv b.i.d. for 2 w, then Acy, 800 mg po q.i.d. for a total of 120 d [82] or 12 w [83]</td>
</tr>
<tr>
<td>[10]</td>
<td>Liver</td>
<td>Preemptive</td>
<td>Gan, 5 mg/kg iv b.i.d. for 7 d for positive results of surveillance shell vial cultures</td>
</tr>
<tr>
<td>[14]</td>
<td>Liver</td>
<td>Preemptive</td>
<td>Gan, 10 mg/kg/d iv, following first positive antigenemia test result for seronegative recipients or ≥100 positive cells per 2 × 10⁵ leukocytes for seropositive recipients. Prophylaxis continued until antigenemia decreased to zero (usually 14 d).</td>
</tr>
<tr>
<td>[84]</td>
<td>Kidney, heart, and liver</td>
<td>Universal (for recipient /donor)</td>
<td>Gan, 5 mg/kg/d iv for 5–10 d, then 1 g po t.i.d. for an additional 12 w</td>
</tr>
<tr>
<td>[69]</td>
<td>Heart</td>
<td>Universal</td>
<td>Gan, 5 mg/kg iv b.i.d. for 2 w, then 6 mg/kg q.d. 5 d/w until day 28</td>
</tr>
<tr>
<td>[25]</td>
<td>Lung</td>
<td>Universal</td>
<td>Gan, 5 mg/kg q.i.d. from day 7 for 2 w, then 5 mg/kg q.d. for 1 w, then 5 mg/kg/d for 5 d/w until day 90</td>
</tr>
<tr>
<td>[28]</td>
<td>Lung</td>
<td>Preemptive</td>
<td>Gan, 5 mg/kg iv b.i.d. for 5 d, then 5 mg/kg/d for a total of 4 w for CMV antigenemia level &gt;25 per 10⁵ leukocytes</td>
</tr>
<tr>
<td>[85]</td>
<td>Kidney</td>
<td>Universal</td>
<td>Gan, 1 g po t.i.d. for 12 w</td>
</tr>
</tbody>
</table>

**NOTE.** Acy, acyclovir; Gan, ganciclovir.
patients. Regardless of the diagnostic criteria or preemptive therapy tool employed, virtually all of these patients would ultimately receive ganciclovir, even if the preemptive approach was applied. The universal prophylactic strategy, therefore, is justifiable for use in this subgroup of organ transplant recipients. Use of said approach with oral ganciclovir, however, is not optimal for organ transplant recipients who require a higher level of immunosuppression [74]. A rising virus load or antigenemia level (beyond 2 weeks) may imply suboptimal suppression and the potential for emergence of ganciclovir resistance.

A vast majority of transplant recipients, however, are not seronegative-recipients of transplants from seropositive-donors; preemptive therapy appears to be the preferable approach for treatment of these patients. Novel anti-CMV drugs are being developed or are undergoing clinical trials. Should the potency and efficacy of future anti-CMV drugs approach those of an ideal agent, the current strategies of prophylaxis would warrant reconsideration.

References

28. Kelly J, Hurley D, Raghu G, the University of Washington Lung Transplant Program. Comparison of the cost effectiveness of preemptive therapy as directed by CMV antigenemia and prophylaxis with ganciclovir in Prophylaxis for CMV in Transplant Recipients • CID 2001;32 (1 March) • 749
68. Valentine HA, Gao S-Z, Menon SG, et al. Impact of prophylactic immediate posttrans-