Cytomegalovirus Viremia in Lung Transplant Recipients Receiving Ganciclovir and Immune Globulin*

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Background: Cytomegalovirus (CMV) disease is an important cause of organ transplant-related morbidity and mortality. During the last 5 years at our institution, prophylactic ganciclovir and hyperimmune globulin have been routinely administered to lung transplant recipients whenever the donor or the recipient was CMV antibody-positive. We sought to assess the efficacy of prophylaxis on viremia, CMV disease, and bronchiolitis obliterans syndrome (BOS).

Methods: A retrospective chart review of 61 consecutive lung transplants performed between recipients between January 1993 and August 1995 was performed. Fifty-six patients who survived at least 1 month were analyzed. Patients were considered at risk for CMV disease whenever pretransplant donor or recipient serology was positive.

Results: Fourteen of the 39 patients at risk (36%) had viremia while on prophylaxis. The rate of CMV disease was 13% during the first 6 months following transplantation. A donor whose CMV serology was positive appeared to increase the risk of BOS in a Cox regression model (relative risk=2.4; 95% confidence interval=0.86-6.74; p=0.0957). Neither age, CMV infection (viremia or a positive specimen from BAL), recipient’s serology at the time of transplantation, or CMV disease was associated with BOS. None of these variables was associated with mortality on Cox regression analysis or univariate analysis.

Conclusions: Administration of combination ganciclovir and hyperimmune globulin prophylactic therapy to lung transplant recipients at risk for CMV infection and disease is associated with a relatively low incidence of disease, which appears only after prophylaxis treatment with ganciclovir is completed. Ganciclovir prophylaxis does not prevent CMV viremia; however, viremia while on prophylaxis is not predictive of disease.

Key words: cytomegalovirus; ganciclovir; hyperimmune globulin; lung transplantation; viremia

Abbreviations: ALG=antilymphocyte globulin; BOS=bronchiolitis obliterans syndrome; CMV=cytomegalovirus; D=donor’s CMV serology at time of transplantation; R=recipient’s CMV serology at time of transplantation; HIG=hyperimmune globulin; NPV=negative predictive value; PPV=positive predictive value

Cytomegalovirus (CMV) infection in lung transplant recipients may lead to acute morbidity and mortality, and it continues to be an impediment to long-term survival. Although acute mortality and morbidity from CMV may be reduced through selection of donors without serologic evidence of CMV and through administration of CMV-negative blood products, these strategies have a limited impact because most candidates have been previously exposed to CMV and the supply of organs is limited. CMV disease has been associated with the use of antilymphocyte globulin (ALG), treatment of steroid-resistant acute rejection episodes, and chronic allograft rejection.

Several strategies have been assessed for prevention of CMV disease in transplant recipients. These include prophylactic administration of antiviral drugs such as acyclovir or ganciclovir. Hyperimmune globulin (HIG) has also been used for prophylaxis, with beneficial results reported in bone marrow, kidney, and lung graft recipients. Nonetheless, its efficacy has been questioned as well as its cost. A randomized, double-blind, placebo-controlled clinical trial failed to show statistically significant reductions in CMV disease among liver transplant recipients, but did show a significant decrease in...
CMV-associated disease. In other studies, prophylactic therapy has demonstrated encouraging results among liver and kidney transplant recipients. Combination therapy of ganciclovir plus HIG has been utilized, although it has not prevented infection in all cases. However, it has repeatedly been shown to delay the appearance of disease.

Interpretation of the various studies is complicated by the definitions used for asymptomatic infection vs disease and the type of the laboratory investigations employed.

As with other solid organ transplants, investigators in the field of lung transplantation have searched for an effective prophylactic regimen. CMV disease has been associated with the bronchiolitis obliterans syndrome (BOS), the clinical manifestation of chronic rejection. In the Toronto Lung Transplant Program, we have administered prophylactic ganciclovir and HIG for 5 years. We have observed the development of CMV-positive blood and BAL specimens while transplant recipients were receiving ganciclovir prophylaxis. We therefore sought to assess the prevalence of this observation and its association to the clinical diagnosis of CMV and to BOS.

**METHODS**

**Study Design**

We conducted a retrospective review of all medical records of lung transplant recipients transplanted between January 1993 and August 1995 at The Toronto Hospital. Data on these patients were being gathered as part of a double-blind clinical trial, still in progress while preparing this manuscript, in which recipients receive induction ALG or placebo for the first 7 days posttransplant.

**Surveillance Protocol**

Scheduled flexible bronchoscopies were conducted at 1, 2, 3, 6, 9, 12, 26, 39, 52, 88, and 104 weeks after transplant. In addition to BAL, three to five transbronchial biopsies from two different lobes were taken during each procedure. CMV shell-vial cultures and antigen detection by immunofluorescence from BAL specimens were done at each visit until week 26. Surveillance spirometry, urine tests, and blood work (hemoglobin, WBC, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, and electrolytes) were performed weekly during the first 2 months and monthly thereafter. Surveillance chest radiographs were taken weekly for the first month, monthly for the first year, and then 2 to 4 times per year. CMV serology was performed on day 1 (IgM) and at weeks 4, 8, 12, 16, 6 months, 9 months, 1 year, 18 months, and 2 years (IgG). Antigenemia and CMV shell-vial culture from buffy coat specimens were done at weeks 2, 4, 6, 8, 10, 12, 14, 16, and 26. Procedures and tests were also ordered when clinically indicated.

**Immunosuppression Protocol**

Recipients received methylprednisolone, 500 mg IV intraoperatively, and were started on cyclosporine, azathioprine, and prednisone immediately postoperatively. Half the patients received ALG for 7 days posttransplant as part of the aforementioned double-blind study. Trough levels of cyclosporine were maintained between 250 and 350 ng/mL during the first 3 months and gradually reduced to 150 to 250 ng/mL after approximately 1 year. Azathioprine was prescribed at a dose of approximately 1 mg/kg/d; the dose was reduced if liver enzyme abnormalities or leukopenia occurred. Prednisone was initially given at approximately 0.5 mg/kg/day and reduced gradually through the first year; after year 1, the dose was 15 mg every other day indefinitely. Episodes of acute rejection were treated with methylprednisolone, 1 g IV daily for 3 days, followed by prednisone, 40 mg daily. The augmented prednisone dose was tapered over 3 to 4 weeks.

If either the donor or the recipient were positive for CMV antibodies as determined by latex agglutination (CMVSCAN; Becton-Dickinson Microbiology Systems; Cockeysville, Md), CMV prophylaxis was administered with anti-CMV HIG, 150 mg/kg at week 1 and 3, then 100 mg/kg every 2 weeks until week 12, and then a final dose at 16 weeks. Ganciclovir, 10 mg/kg/d, was given IV for 2 weeks, and then a dose of 5 mg/kg/d was given IV three times per week until week 12.

**Diagnosis of CMV Disease**

CMV disease was diagnosed when histopathologic examination demonstrated inclusion bodies in transbronchial biopsy, open lung biopsy, BAL, or autopsy specimens.

**Bronchiolitis Obliterans Syndrome**

BOS was graded according to the classification system of Cooper and colleagues.

**Statistical Analysis**

Kaplan-Meier curves, log-rank tests, and Cox proportional hazards regression models were used for analysis. Age, sex, donor and recipient's pretransplant CMV serologic status, viremia, CMV disease, and results of CMV studies in BAL fluid were used to model Cox proportional hazards regressions for BOS and mortality as outcomes. Categorical variables were coded as 1 or 0 for positivity or negativity, respectively. The models were tested for proportionality and fitness. Proportionality was tested by including a time-dependent covariate in the model, and fitness was tested by residual plot analysis. An overall 95% confidence level was used and all tests were two-tailed. Analyses were done using SAS® software (SAS Institute; Cary, NC).

**RESULTS**

**Recipient Demographics**

Of the 61 lung transplant recipients, 56 survived beyond 1 month and have been included in the analysis (mean age, 42.3±13 years; range, 21 to 66 years; 26 women [46%] and 30 men [54%]). The mean follow-up period was 21.4±10.7 months (range 1.1 to 38.2 months). Underlying diseases and serologic status of the donors and recipients are shown in Tables 1 and 2. The 39 subjects who were CMV-seropositive or had a CMV-seropositive donor received prophylaxis for CMV. None of the five...
recipients who were excluded due to early mortality (ie, <30 days) died from CMV infection or factors secondary to CMV infection.

Survival

For all 61 transplant recipients, the probability of surviving 24 months was estimated at 75%. Of the 56 recipients included in the study, 10 died during follow-up. Two of these deaths were related to CMV disease. One of the deaths was attributed to pneumonia and the other one to sepsis. Neither age, gender, CMV infection, donor’s serology, recipient’s serology at the time of transplantation, or CMV disease was associated with mortality on Cox regression analysis.

Viremia

CMV was recovered from blood at least once in 21 of 56 subjects (38%). During the first 12 weeks posttransplant, 11 of 39 recipients (28%) at risk of CMV who were receiving prophylaxis with ganciclovir and HIG had a first episode of viremia. By week 16, 14 of 39 recipients (36%) on prophylaxis had shown viremia. The cumulative incidence of viremia during the first 6 months was 41% (16 of 39 patients) among those who received prophylaxis. By week 12, 11 of the 16 patients (69%) who had ever shown viremia during the first 6 months had done so; by week 16, 14 of 16 patients (88%) showed viremia. Viremia occurred in 5 of 17 donors’ CMV-negative serology/recipients’ CMV-negative serology (D−/R− patients) (29%), all during the first 12 weeks posttransplant while receiving acyclovir prophylaxis for herpes simplex virus. Of note, one of these five patients had received a CMV-positive blood product posttransplant. There were no significant differences in the rates of viremia when compared by initial serologic status (log-rank test, p=0.0582; Fig 1).

Bronchoalveolar Lavage

Thirty-one of 56 patients (55%) had positive cultures for CMV at least once from their BAL fluid. Seventeen of the 21 patients who were ever viremic had at least one positive BAL (in 5 patients, simultaneously with their first viremia). During the first 12 weeks posttransplant, the first BAL was positive in 2 of 39 at-risk patients on prophylaxis. Viremia was also documented in both patients before week 12. The rate of CMV recovery in BAL specimens increased shortly after finishing the ganciclovir prophylaxis administration period. By week 16, 14 of the 31 recipients (45%) who ever showed CMV in BAL had done so. The cumulative incidence of positive BAL cultures during the first 6 months was 69% (27 of 39 patients) who had received prophylaxis. By week 12, only 2 of 27 patients (7%) who ever shed CMV in BAL fluid during the first 6 months had done so; by week 16, 12 of 27 patients (45%) had done so. Four patients in the D−/R− group had a positive BAL culture; they all showed viremia. The proportion of patients with a BAL specimen that was positive for CMV was significantly smaller among the D−/R− patient group (log-rank test, p=0.0017; Fig 2). Cumulative incidences of both viremia and positive BAL cultures are illustrated in Figure 3.

The cumulative incidence of CMV infection among recipients at risk was 77% (30 of 39 patients); CMV was recovered from both blood and BAL specimens in 13, blood only in three, and BAL fluid only in 14 patients.

CMV Disease

Among the 39 patients who received CMV prophylaxis, five had histologic evidence of CMV disease (four transbronchial biopsy specimens and one autopsy). The five cases are described in Table 3. CMV was found at autopsy in a patient whose blood, BAL, and open lung biopsy specimens had been negative for CMV. None of these five patients had detectable viremia before the disease was diagnosed. Four of them had had positive BALs. Three patients were asymptomatic. One of them had leukopenia 1 week before the positive biopsy. Another lung transplant recipient had histologic evidence of CMV pneumonitis 15 weeks after transplant and received treatment with ganciclovir. This patient developed GI bleeding and intestinal pseudo-obstruction 1 year

Table 1—Reason for Lung Transplantation in 56 Recipients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>Emphysema</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Eisenmenger’s syndrome</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Broncholitis obliterans</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2—CMV Serology in Recipients and Donors

<table>
<thead>
<tr>
<th>Serology</th>
<th>No. of recipients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R−/D−</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>R+/D−</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>R−/D+</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>R+/D+</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>
later; toxic megacolon and pseudomembranous colitis subsequently were diagnosed. Both *Clostridium difficile* toxin and CMV antigenemia tests were positive. The fourth patient complained of fatigue as the only symptom. The fifth patient had an episode of pneumonia 1 month after transplant. He had a
turbulent clinical course and died 2 months later. The autopsy revealed disseminated CMV disease involving the lungs, kidneys, adrenal glands, pancreas, spleen, and liver. The serologic status of the five recipients and their donors were: D−/R− (n=2), D+/R− (n=2), and D+/R+ (n=1).

The median time to disease was 109 days (range, 102 to 178 d). Overall, 38% of recipients developed viremia. Viremia was not predictive of CMV disease nor was it a sensitive marker for disease (sensitivity, 0%; specificity, 53%; positive predictive value [PPV], 0%; negative predictive value [NPV], 78%). Fifty-five percent of recipients had at least one BAL culture that was positive for CMV. A positive BAL was not predictive of disease, whereas a negative BAL for CMV had a very high NPV (sensitivity, 80%; specificity, 32%; PPV, 15%; NPV, 92%). The patients whose BAL became positive once prophylaxis was stopped did not become symptomatic. The patients who were viremic while on prophylaxis were asymptomatic and therefore were not treated, with the exception of those with positive histologic evidence of CMV disease.

**Bronchiolitis Obliterans Syndrome**

Among the recipients surviving at least 3 months (n=52), 18 patients (33%) received a diagnosis of BOS. Eleven of the 18 patients (61%) tested positive for CMV in BAL fluid prior to the diagnosis of BOS. Six of the 11 also tested positive in blood before the BOS diagnosis. Analysis using Cox regression models with BOS as the outcome variable identified positive serology in a donor as the only risk factor (relative risk, 2.4; 95% confidence interval, 0.86 to 6.74; p=0.0957). An inclusion criterion of p=0.1 was used. There was no evidence of nonproportionality of the hazard. The residual plots analysis supported the appropriateness of the model. Recipient’s age, gender, CMV serology before transplantation, viremia, BAL positive for CMV, and CMV disease were not associated on Cox regression with the development of BOS during a mean follow-up of 21 months.

**DISCUSSION**

The incidence of CMV disease among solid organ transplant recipients receiving prophylactic therapy with acyclovir, ganciclovir, and HIG either alone or in combination (usually reported for the first 6 months after transplant) ranges from 5% to 30% for kidney transplants,4,7,9,12,15,17 from 9% to 30% for heart,5,28 and from 0.8% to 19% for liver.12,14,15,29 Increased incidences of disease have been reported in the highest risk group (D+/R−) among renal graft recipients (60%)

![Figure 3. Overlaid Kaplan-Meier curves showing the cumulative incidence probabilities of viremia and a BAL positive for CMV. The inset shows the number of patients at time of transplantation (0 months) and 12 months thereafter. The vertical line at 3 months shows when prophylaxis therapy was stopped.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21763/)
Table 3—Summary of the Five Cases With Positive Histopathology for CMV

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>R/D</th>
<th>BAL CMV</th>
<th>Viremia</th>
<th>Time to Positive Histopathology</th>
<th>Antiviral Therapy*</th>
<th>Clinical Picture</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>M</td>
<td>+/+</td>
<td>+</td>
<td>−</td>
<td>15 wk (107 d)</td>
<td>Y</td>
<td>Fatigue as only complaint. No fever. No other symptoms or signs.</td>
</tr>
<tr>
<td>48</td>
<td>M</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>25 wk (180 d)</td>
<td>Y</td>
<td>Asymptomatic. Leukopenia 7 days before the positive results. No symptoms or signs.</td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>−/+</td>
<td>+</td>
<td>−</td>
<td>25 wk (174 d)</td>
<td>Y</td>
<td>Asymptomatic. Ten months later an iron deficiency anemia was diagnosed. GI bleeding was shown; patient developed disseminated intravascular coagulation and died. Pseudomembranous and CMV colitis were diagnosed.</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>+/−</td>
<td>+</td>
<td>−</td>
<td>16 wk (110 d)</td>
<td>Y</td>
<td>Admitted 1 month after transplant because of pneumonia. Active investigation including an open lung biopsy failed to yield an etiologic agent. Despite empirical therapy, the patient’s condition progressively worsened and he died. Autopsy specimens showed typical CMV inclusions in lung, liver, kidneys, adrenal glands, pancreas, and spleen.</td>
</tr>
<tr>
<td>39</td>
<td>M</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
<td>14 wk (104 d)</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

*14-day IV ganciclovir cycle at 5 mg/kg bid.

(65%);21 Maurer et al16 reported incidences of 29%, 67%, and 41% for lung-transplant patients receiving three different prophylaxis regimens. Ettinger and colleagues20 recorded a 75% disease incidence among 36 lung transplant patients, 7 of whom received combination prophylactic therapy with ganciclovir and HIG for 2 to 3 weeks. Gould et al31 reported CMV disease in 10 out of 59 patients (17%) surviving more than 4 weeks after lung transplant. Our 13% incidence among 39 patients is low compared to previous reports. However, the definitions of CMV disease vary across different studies; therefore, direct comparisons may not necessarily be valid. Moreover, as Chamberlain32 pointed out, defining CMV pneumonia based on anatomic findings, although widely done, limits the sensitivity and specificity of methods like transbronchial biopsy and BAL.

Our median time to CMV disease exceeded 100 days. Three of five cases of CMV disease occurred before the last dose of HIG, but shortly after the last combined dose of ganciclovir and HIG. These observations support a delay in the appearance of disease as a consequence of viral prophylaxis.21 The observed time to disease in this study appears longer than in previous reports. Others have observed times of 78 days after liver transplantation,18 81 days after bone marrow transplantation,20 and 46 days after lung transplantation.19 Kelly and collaborators33 administered prophylactic ganciclovir to 21 lung allograft recipients for 6 weeks. They diagnosed CMV disease in 8 patients (mean follow-up of 430 days); six cases were diagnosed before day 100. Our results are in agreement with the report by Goodrich and coworkers34 in bone marrow transplant recipients. Among the 37 bone marrow transplant recipients receiving prophylaxis, only one developed CMV disease before day 100, compared with 15 of 35 patients receiving placebo. However, the time to disease in our population was not as long as that noted by Zamora et al10 (201 days among 19 patients who received one dose of HIG biweekly for a total of three doses, plus 1 month of IV ganciclovir followed by 5 months of oral acyclovir).

Preemptive therapy was proposed based on the assumption that urine, blood, and/or BAL tests for CMV are predictive of CMV disease.13,14,34,35 The diagnosis will be influenced by the ability of the test to detect clinical disease. For example, it is possible that some of the donor/recipient CMV-negative pairs in our study represented false-negative results from the method used to assess CMV serology, although serology had little to do with the decision to initiate treatment for disease. Viremia is perhaps more relevant. In bone marrow transplant recipients, Meyers and colleagues35 observed viremia in 21%. Viremia had a PPV of 60% for CMV disease. It has been argued that the value of preemptive therapy is dependent on the sampling frequency and assay sensitivity.24 Paradoxically, in our study, viremia was not apparent before CMV disease in any of our patients on prophylaxis; five out of 23 patients without viremia developed CMV disease, whereas none of the 16 patients who had showed viremia developed disease (PPV, 0%). Specificity (53%) and NPV (78%) were somewhat higher. In an attempt to improve the yield of viral detection tests in blood, Egan et al36 tested the hypothesis that higher levels of antigenemia might be better for CMV disease prediction. Despite this modification, they found a PPV of only 46%, although the NPV was 100%. With regard to BAL shell-vial cultures, our sensitivity was higher (80%), with a relatively low PPV (15%). Specificity was low (32%) and NPV was high (92%).
This is not surprising, since a diagnostic test’s performance is best when the pretest probability of disease is in the range of 40% to 60%.\textsuperscript{37} When prevalence decreases, sensitivity and PPV tend to fall.\textsuperscript{37} Conversely, specificity and NPV tend to increase.\textsuperscript{37} Thus, the usefulness of CMV testing will vary according to management protocols such that positive CMV detection by culture or antigenemia is dependent on the antiviral protocol in use and therefore clinically relevant in patients not receiving CMV prophylaxis.

Not only was the presence of viremia of little diagnostic value in our study, but the majority of first detectable episodes of viremia occurred while patients were receiving CMV prophylaxis. Martin et al\textsuperscript{18} reported results of a study on antiviral drugs in the prevention of CMV disease among liver transplant recipients. Most CMV disease episodes occurred while patients received prophylaxis. Winston et al\textsuperscript{29} showed ganciclovir to have a significant effect in decreasing the incidence of infection and CMV disease among liver graft recipients. Nonetheless, those patients who developed either infection or disease did so while taking prophylactic drugs.

As opposed to viremia, most positive BAL fluid cultures occurred after prophylactic ganciclovir administration was completed but before the last dose of HIG (after week 12). The diagnostic utility of a positive BAL culture was poor. However, its NPV was high. The high false-positive yield of BAL has resulted in authors ignoring such results in asymptomatic patients (eg, patients who had positive BALs were not considered infected).\textsuperscript{36} Dunn et al\textsuperscript{3} did not consider a positive test result (viral culture or antigen shedding) in asymptomatic patients a failure of prophylaxis. Storch et al\textsuperscript{30} studied quantitative methods in BAL viral culture and found that even though the correlations between higher viral titers in BAL and infection and disease appeared to be better, the PPV was still poor.

Another issue with instituting a broad strategy for prophylactic ganciclovir administration is the potential for viral resistance. Drew et al\textsuperscript{40} studied viral resistance in people with AIDS. Among those treated with ganciclovir for more than 3 months, 8% excreted ganciclovir-resistant CMV strains, whereas resistant strains were not recovered from 31 patients before treatment, nor from 7 patients treated for up to 3 months. Boivin et al\textsuperscript{41} studied the sensitivity of CMV viruses isolated from 42 solid organ transplant patients and found no resistant strains. Thus, at least to date, the risk of selecting ganciclovir-resistant strains among transplant recipients and AIDS patients appears low when prophylactic or treatment regimens are given for 3 months or shorter.

Keenan et al\textsuperscript{38} reported on an increased relative risk for development of obliterative bronchiolitis when CMV infection and positive donor’s serology were present. They also mentioned that their finding failed to reach statistical significance (at the 95% level). The Stanford group reported also that “cytomegalovirus positivity” was the only risk factor for obliterative bronchiolitis approaching statistical significance on univariate analysis; however, no risk factors were identified on multivariate analysis.\textsuperscript{42} The only risk factor for BOS approaching significance we identified was having a CMV-positive donor.

It is becoming increasingly apparent that prophylactic ganciclovir prevents or delays CMV disease among lung recipients. Critical questions remain as to whether the costs and benefits of prophylactic therapy outweigh the costs and benefits of repeatedly testing patients at risk and preemptively treating them. Based on the literature, patients may develop disease without previously having shed viruses\textsuperscript{13,34} and hence would not be diagnosed and treated until overt disease had developed. Considering that CMV disease is associated with significant morbidity and mortality and CMV disease appears infrequently while transplant recipients receive prophylaxis, prophylactic intervention with ganciclovir and HIG is a reasonable approach to preventing CMV disease.

In summary, our data suggests that blood and BAL shell-vial culturing with immunofluorescence antigen detection for CMV is not useful as a screening tool for the diagnosis of CMV disease when used in patients receiving combination CMV prophylaxis. The presence of viremia in patients not receiving prophylaxis must be interpreted differently from viremia in patients receiving prophylaxis. Combination prophylactic therapy efficiently prevents early CMV disease and decreases the incidence of disease. A high incidence of CMV colonization and disease was detected among the low-risk D−/R− group. Extra care is required to prevent primary CMV infection and disease in this group. In addition, when analyzing the results of our prophylaxis protocol, neither CMV infection nor disease predicted BOS. A positive donor serology appeared as the only factor which increased the risk of BOS. We conclude that administration of prophylactic ganciclovir plus HIG is a useful approach to the clinical scenario where either the donor or recipient has serologic evidence of previous CMV infection. The utility of routine testing for CMV in the absence of evidence of disease is limited when such prophylaxis is prescribed. Further studies are required to assess whether HIG provides an incremental benefit to lung transplant recipients receiving ganciclovir.
REFERENCES


