Infections in Renal Allograft Recipients: A Review of the Philippine Experience

Myrna T. Mendoza, MD,* Rosemarie R. Liquete, MD,* Enrique T. Ona, MD,* and Filoteo A. Alano, MD*

ABSTRACT

Objective: To determine frequency and types of infections developed by renal allograft recipients following transplantation and to relate these to their immunosuppressive therapy.

Design: Descriptive, prospective study.

Methods: At the National Kidney Institute (NKI), 513 kidney graft recipients were followed for 1 year for hospital admissions due to infectious disease. All patients were free of active infection before transplantation. Criteria for the diagnosis of infection after transplantation, including fever work-up, were provided in transplant protocols. Patients were given double or triple immunosuppressive regimens.

Results: Infection was highest during the first 3 months following transplantation. Bacterial and viral infections were noted early, whereas fungal infections and tuberculosis occurred later in the first year following transplantation. Pneumonia and urinary tract infections were the most common bacterial infections observed. Amoebiasis and malaria were observed more in patients on cyclosporine and triple regimens. Nocardiosis occurred more frequently among patients on azathioprine.

Conclusion: More tropical infectious diseases were observed. Early reduction of prednisone in the triple regimen resulted in more rejection episodes but less infection episodes. Rejection therapy influenced the outcome of post-transplant infections.

Key Words: Philippines, transplant infections


Following an organ transplant, immunosuppressive therapy designed to prevent the rejection of the graft, may also prevent the normal immune response to infection. Reports on the frequency and pattern of infections after an organ transplant have primarily originated from developed countries.1-3 There are a few reports from developing countries, especially from the tropics, on infectious complications of transplantation.4-7

Although the first kidney transplant in the Philippines was performed more than 20 years ago, full support and implementation of the transplantation program started only in 1983. At the National Kidney Institute (NKI), the primary transplant center in the country, 1019 kidney transplants have been performed in 1008 recipients, as of December 1994. Five hundred thirteen of these recipients were prospectively followed for at least 1 year following transplantation for hospital admission due to infectious disease, to determine frequency and types of infections they developed and to relate these to their immunosuppressive therapy.

MATERIAL AND METHODS

Pretransplant Protocol

At the start of the transplant program, algorithms and protocols were provided to house staff physicians for work-up of common infectious disease problems before and after transplant and for adjustment of immunosuppressive regimens.

The transplant protocol at the NKI required that both donor and recipient be free of infection at the time of transplant. Donors positive for hepatitis B surface antigen (HBSAg) and with abnormal liver function tests were disqualified. Recipients who were hepatitis B virus (HBV) carriers were not disqualified. Anti-hepatitis C virus (anti-HCV) tests were not done because the test became available in the country only in 1994. Recipients excluded from the transplant program were those over 60 years of age and those with chronic active hepatitis. Pretransplant serologies were also done for cytomegalovirus (CMV) and Epstein Barr virus (EBV). Transplant surgery was deferred for recipients with active pulmonary tuberculosis (TB) until after 2 months of intensive therapy and sputum conversion; maintenance therapy was continued after transplant.

Patients with a history of adequate anti-TB treatment, positive PPD, and with scarring or calcified infiltrates shown on chest x-ray were given isoniazid prophylaxis.
following transplantation. Prophylactic antibiotics were given during transplant surgery only. Cotrimoxazole prophylaxis was given for 1 month after transplant when cyclosporine dose was reduced to 4 mg/kg per day.

Immunosuppressive Protocol

A total of 513 patients were included in the study. Seventeen percent of those on double therapy, 22% on triple therapy, and 20% on triple low-dose prednisone received cadaver kidneys. These patients were divided into three immunosuppressive protocols. The first group received the double therapy of either azathioprine (AZA) or cyclosporine (CYA) plus prednisone (Pred), and the second group received triple therapy of AZA, CYA, and Pred during the first 3 months following transplantation. Prednisone doses were similar in the first two groups. The third group of patients also received the triple regimen, but with a lower dose of prednisone than the first and second groups during the first 3 months following transplantation. Prednisone dose was reduced to 0.5 mg/kg per day as early as 1 week after transplant in the third group of patients. At 4 months after transplant, all patients were converted to AZA/Pred immunosuppression except for some who could afford to continue on CYA or could not tolerate AZA. In general, acute rejections were treated with pulse steroid therapy. OKT3 was used in only five patients who could afford it.

Diagnosis of Infection

Infection after transplant was diagnosed when two or more of the following conditions were met: (1) positive culture of a pathogen from urine (>100,000 colonies/mL); (2) x-ray and physical findings indicative of infection; (3) fever over 38°C; (4) antibiotic treatment for confirmed infection as judged by the authors (attending physicians); and (5) post-mortem or surgical biopsy specimens positive for infection.

When an infection was identified, further information regarding dose of immunosuppressive regimen, prior rejection episodes, and outcome were also noted. Some patients had more than one type of infection at a time. When different pathogens were found in different sites, each was considered as a separate episode of infection.

RESULTS

The pretransplant seroprevalence rates in the study population were as follows: CMV positive, 99%; EBV, 95%; and HBV, 52%. The HBsAg carrier rate was 8.3%.

The occurrence of infection was highest during the first 3 months following transplantation; 54% of the patients had one or more infections during this interval. Subsequently, the infection rate declined to 23% at 4 to 6 months and 13% at 7 to 9 months after transplantation. During the 10 to 12 months following transplant, the infection rate was only 10%.

Pattern of Infection

The pattern of infections observed is shown in Table 1. In the first 3 months following transplantation, bacterial infections accounted for 76% of the total infections that developed. This was followed by viral and parasitic infections at 10% each. Four to six months after transplant, fewer bacterial infections (57%) were observed; 14% were due to tuberculosis and 8% were due to Nocardia. Toward the ninth month, more viral and fungal infections were noted. More cases of nocardiosis (12%) were observed toward the end of the first year after transplantation.

Pneumonia and urinary tract infection (UTI) were the most frequent bacterial infections seen. Klebsiella pneumoniae was the most common cause of pneumonia, and Escherichia coli was the most common cause of UTI. Salmonella caused 23% of the bacteremias. Other bacterial infections observed were skin and soft tissue infections and gastroenteritis.

Definite viral infection episodes were due to CMV (17 cases), herpes zoster (13 cases), herpes simplex (13 cases), varicella (10 cases), and hepatitis (10 cases). Epstein-Barr virus was seen in only two patients.
Most of the observed parasitic infections were intestinal amoebiasis (13 cases) and malaria (9 cases). *Pneumocystis carinii* pneumonia (PCP) was seen in only four patients, all while on cyclosporine. Five female patients had trichomoniasis and one patient had giardiasis. Tuberculosis developed in 20 patients and 7 had disseminated disease. Nocardiosis was seen in 18 patients. The deep-seated or systemic fungal infections seen were mucormycosis (6), cryptococcosis (4), disseminated candidiasis (3), and aspergillosis (3).

### Relation between Immunosuppressive Therapy and Infections

No clear relation to type of immunosuppressive therapy was noted, although bacterial infection seemed to be more common in patients receiving both azathioprine and cyclosporine. More tuberculosis and more fungal and parasitic infections occurred in patients receiving cyclosporine (Table 2). Nocardiosis more commonly occurred in patients on azathioprine.

Since pneumonia and UTI accounted for more than 60% of the bacterial infections, only these two infections were considered in relation to immunosuppressive regimens (Table 3). The proportion of these infections was lower with double than with triple therapy. However, statistical comparison using chi-square test showed that there was no significant difference in pneumonia episodes between regimens. The proportion of UTI was lowest in patients on triple regimen with lower dose prednisone. This was significant at P < 0.01. To find out if the difference was due to rejections or rejection therapy, rejection episodes were compared (Table 4). Double and triple regimens had equal total rejection episodes (21%). The rejection rate was 30% in the triple regimen with low dose prednisone group. Rejection episodes in this third group was also higher even within 3 months after transplantation (P < 0.05). But it was in this group that UTI episodes were lowest. No correlation between rejection and bacterial infections was observed.

### Mortality

Thirty-five deaths were directly attributed to infection, with an overall mortality of 7%. The proportion of those who died among the total patient population was analyzed according to the immunosuppressive protocol used (Table 5). Mortality was highest (11.7%) among those on triple regimen. Fifty-five percent of the mortalities occurred within the first 3 months after transplantation, and 25 to 33% followed acute rejection therapy with high dose steroids. The three major causes of death were septicemia (10), bacterial pneumonia (9), and systemic fungal infection (5). Three patients with CMV pneumonia died with concomitant infection, two with pulmonary nocardiosis, and one with salmonellosis. One patient with

---

**Table 2.** Distribution of Types of Infections according to Immunosuppressive Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>AZA + Pred</th>
<th>CYA + AZA + Pred</th>
<th>CYA + Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic fungal</td>
<td>3 (2)</td>
<td>5 (2)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Viral</td>
<td>4 (2)</td>
<td>17 (17)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7 (3)</td>
<td>7 (3)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Nocardiosis</td>
<td>13 (6)</td>
<td>3 (1)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Parasitic</td>
<td>4 (2)</td>
<td>11 (6)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>148 (70)</td>
<td>193 (82)</td>
<td>89 (68)</td>
</tr>
</tbody>
</table>

AZA = azathioprine; Pred = prednisone; CYA = cyclosporine.

**Table 3.** Bacterial Infections among Patients on Post-transplant Immunosuppressive Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Pneumonia</th>
<th>UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double</td>
<td>139</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Triple</td>
<td>214</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td>Triple low dose</td>
<td>160</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

UTI = urinary tract infection.

**Table 4.** Rejection Episodes among Patients with Double and Triple Immunosuppressive Therapy

<table>
<thead>
<tr>
<th>Immunosuppressive Therapy</th>
<th>Double n (%)</th>
<th>Triple n (%)</th>
<th>Triple LD Prednisone n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>139</td>
<td>214</td>
<td>160</td>
</tr>
<tr>
<td>Episodes of rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>within (mo):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>17 (12.2)</td>
<td>21 (9.8)</td>
<td>25 (15.6)</td>
</tr>
<tr>
<td>4-6</td>
<td>6 (4.3)</td>
<td>8 (3.7)</td>
<td>9 (5.6)</td>
</tr>
<tr>
<td>7-9</td>
<td>1 (0.7)</td>
<td>7 (3.3)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>10-12</td>
<td>6 (4.3)</td>
<td>9 (4.2)</td>
<td>8 (5.0)</td>
</tr>
<tr>
<td>Total rejections</td>
<td>30 (21.5)</td>
<td>45 (21.0)</td>
<td>48 (30.0)</td>
</tr>
</tbody>
</table>

**Table 5.** Fatal Infections Associated with Rejection Therapy

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Double n (%)</th>
<th>Triple n (%)</th>
<th>Triple LD Prednisone n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>139</td>
<td>214</td>
<td>160</td>
</tr>
<tr>
<td>Mortality</td>
<td>6 (4.3)</td>
<td>25 (11.7)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Mortality with rejection</td>
<td>2 (1.5)</td>
<td>8 (3.7)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*65% of deaths occurred within the first 3 months after transplantation. LD = low dose.
initial PCP died with mucormycosis. Two died of fulminant HBV; both were positive for HBsAg pretransplant.

DISCUSSION

The pattern of infections observed among the renal transplant patients studied was similar to that reported from other transplant centers. Infections were more frequent during the period when immunosuppression was greatest (i.e., in the first 3 months following transplant surgery). Bacterial infections due to common pathogens and viral infections predominated in the early post-transplant period. Fungal and TB infections occurred 6 months or later in the first post-transplant year. Such observations were also noted in earlier reports that describe the types of pneumonia observed in renal transplant patients.

The triple combination of AZA, CYA, and Pred seemed to favor more bacterial infections.

In contrast to other reports, there was a higher incidence of tropical diseases, such as amoebiasis, malaria, and tuberculosis, which probably reflects the prevalence of these diseases in the country. These were more commonly seen in patients receiving cyclosporine.

Except for HCV, the seroprevalence to CMV, EBV, and HBV before transplantation reflects the seroprevalence in the general Filipino population. Cytomegalovirus reactivation was seen as co-infection in the infections observed. The three patients who died with CMV pneumonia did not receive ganciclovir, because the drug was not yet available.

Another type of infection that was observed to be common among the patients on azathioprine was nocardiosis. Although the majority of cases presented as pulmonary infection, other manifestations also were seen. Nocardiosis presenting as subcutaneous abscesses, brain abscess, and bacteremia were reported in 47 cases.

The association of graft rejection and its therapy to infection have long been described. Bacterial infections follow high dose steroid pulse therapy, whereas viral infections, such as CMV and hepatitis are seen after OKT3 and antithymocyte globulin (ATG) therapy. Although no direct relation to rejection was observed, an association with antirejection therapy was noted in 25 to 33% of the fatal infections in this study. Mortality due to infection was lowest in the group of patients who received the triple regimen with lower dose prednisone. This may mean that the infections in these patients on lower dose prednisone were less severe.

Owing to financial constraints, the immunosuppressive regimen used in the patients studied may be short of the ideal, but with improvements in the dosing regimen of the triple therapy, especially the prednisone dose, severe and fatal infections have been reduced.

REFERENCES